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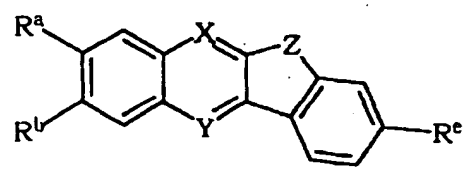
(54) Title: NON-STEROIDAL, TETRACYCLIC COMPOUNDS FOR ESTROGEN-RELATED TREATMENTS



(I)

(57) Abstract: The invention provides non-steroidal estrogenic compounds with estrogenic and anti-estrogenic compounds effects for treatment of estrogen-deficiency related disorders, which compounds are having formula (I) wherein, one of R^a or R^b is 'R^c; R^c and 'R^c are OH, optionally independently etherified or esterified; X is N or -C(R^1)-, wherein R^1 is H, halogen, CN, optionally substituted aryl, (1C-4C)alkyl, (2C-4C)alkenyl, (2C-4C)alkynyl or (3C-6C)cycloalkyl, which alkyl, alkenyl, alkynyl and cycloalkyl groups can optionally be substituted with one or more halogens; Y is N or -C(R^2)-, with the proviso that X and Y are not both N, wherein R^2 has the same meaning as defined for R^1; Z is C(R^3,'R^3)- or -C(R^4,'R^4)-C(R^5,'R^5)-, wherein R^3, 'R^3, R^4, 'R^4, R^5, and 'R^5, independently are H, (1C-4C)alkyl, (2C-4C)alkenyl or (3C-6C) cycloalkyl, which alkyl, alkenyl and cycloalkyl groups can optionally be substituted with one or more halogens. These compounds are useful for estrogen-receptor related treatments in view of a desirable profile of activity for estrogen α and estrogen β receptors.

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NON-STEROIDAL, TETRACYCLIC COMPOUNDS FOR ESTROGEN-RELATED TREATMENTS

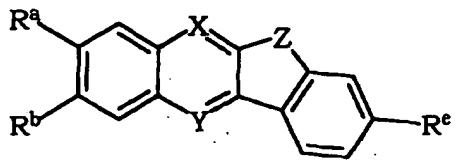
The invention is in the field of non-steroidal compounds for estrogen-related treatments. Estrogenic and anti-estrogenic compounds have a generally recognised utility for estrogen-receptor related medical treatments, such as those for contraception and for treatment of menopausal complaints, osteoporosis, and estrogen dependent tumour control.

More precisely, the invention pertains to non-steroidal estrogen receptor modulating compounds with an 11*H*-Benzo[*b*]fluorene, an 11*H*-Indeno-[1,2-*b*]quinoline, a benz[*a*]anthracene or analogous skeleton. Analogous compounds with claimed usefulness in estrogen related medical treatments are described in US 5,688,808 (1*H*-indeno[1,2-*g*]quinolines) and Morreal et al., J.Med.Chem., 1982, Vol 25, pp 323-326 (benz[*a*]anthracenes). Related estrogen receptor modulating compounds are described in EP 524, 742, EP 832 881 and US 5,147,880 (1*H*-benzo[*a*]fluorenes].

Whereas further improvements for treatment of estrogen-related diseases remains desirable and there is a keen interest in compounds with affinity for the estrogen receptor, new compounds with an 11*H*-Benzo[*b*]fluorene, an 11*H*-Indeno-[1,2-*b*]quinoline, a benz[*a*]anthracene or analogous skeleton and affinity for the estrogen receptor cannot be learnt from these documents. The interest in new compounds with affinity for the estrogen receptor stems from unsatisfactory results with known estrogenic compounds for osteoporose treatment and treatment of other postmenopausal complaints and from the discovery of two distinct types of receptors, denoted ERα and ERβ (see Mosselman et al., FEBS Letters 392 (1996) 49-53 as well as EP -A- 0 798 378). Since these receptors have a different distribution in human tissue, the finding of compounds which possess a selective affinity for either of the two is an important technical progress, making it possible to provide an improved and/or more selective treatment in the field of estrogen-receptor related medical treatments, such as those for contraception and for treatment of menopausal

complaints, osteoporosis, and estrogen dependent tumour control, with a lower burden of estrogen-related side-effects.

This invention provides new tetracyclic non-steroidal compounds having the formula I



Formula I

wherein,
one of R^a or R^b is $'R^e$;
R^e and $'R^e$ are OH, optionally independently etherified or esterified;
X is N or $-C(R^1)-$, wherein R^1 is H, halogen, CN, optionally substituted aryl, (1C-4C)alkyl, (2C-4C)alkenyl, (2C-4C)alkynyl or (3C-6C)cycloalkyl, which alkyl, alkenyl, alkynyl and cycloalkyl groups can optionally be substituted with one or more halogens;
Y is N or $-C(R^2)-$, with the proviso that X and Y are not both N, wherein R^2 has the same meaning as defined for R^1;
Z is $-C(R^3,'R^3)-$ or $-C(R^4,'R^4)-C(R^5,'R^5)-$, wherein R^3, $'R^3$, R^4, $'R^4$, R^5, and $'R^5$, independently are H, (1C-4C)alkyl, (2C-4C)alkenyl or (3C-6C) cycloalkyl, which alkyl, alkenyl and cycloalkyl groups can optionally be substituted with one or more halogens.

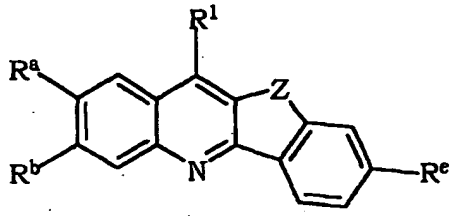
The compounds of this invention have surprising and often selective interactions with estrogen receptors.

The reference to the meanings of R^1 in the definition of R^2 does not imply that R^1 is the same as R^2 in a compound as defined above. In fact, a more specific embodiment of this invention is a compound wherein at least one of R^1 or R^2 is halogen or fluorine substituted methyl.

Depending on the selection of a meaning of R^3, $'R^3$, R^4, $'R^4$, R^5 and $'R^5$, compounds of the invention can have asymmetrically substituted atoms

and can exist in enantiomeric pure forms or mixtures of enantimers differing from the usual 50/50 proportion.

Another specific embodiment of the invention is a compound according to formula I wherein X is $-C(R^1)-$ and Y is N, having the formula II:



Formula II

wherein,

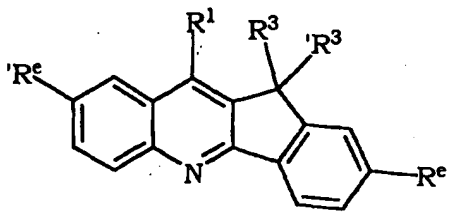
one of R^a or R^b is $'R^e$;

R^e and $'R^e$ are OH, optionally independently etherified or esterified;

Z is $-C(R^3,'R^3)-$ or $-C(R^4,'R^4)-C(R^5,'R^5)-$, wherein R^3, $'R^3$, R^4, $'R^4$, R^5, and $'R^5$, independently are H, (1C-4C)alkyl, (2C-4C)alkenyl or (3C-6C) cycloalkyl, which alkyl, alkenyl and cycloalkyl groups can optionally be substituted with one or more halogens.

A preferred variant of this embodiment is R^a is $'R^e$ and consequently R^b is H and further meanings are as defined for Formula II above. More preferred is R^1 is halogen or fluorine substituted methyl.

Compounds according to formula II in which Z is $-C(R^3,'R^3)-$, R^a is $'R^e$ and R^b is H have the formula III

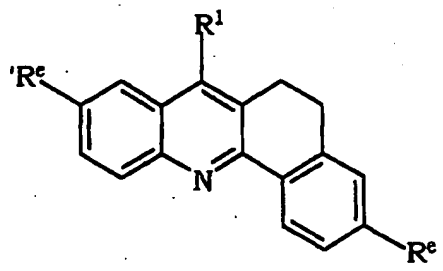


Formula III

whereby the symbols have the meaning as defined for Formula II.

Such compounds are named 11H-indeno[1,2-*b*]quinolines according to the convention of the chemical abstracts.

An embodiment of the invention is a compound according to Formula II, in which Z is $-C(R^4,'R^4)-C(R^5,'R^5)-$; R^a is $'R^e$; R^b, R^4, $'R^4$, R^5 and $'R^5$ are H, having the formula IV

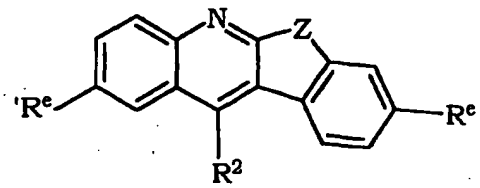


Formula IV

wherein,

R^1 is H, halogen, CN, optionally substituted aryl, (1C-4C)alkyl, (2C-4C)alkenyl, (2C-4C)alkynyl or (3C-6C)cycloalkyl, which alkyl, alkenyl, alkynyl and cycloalkyl groups can optionally be substituted with one or more halogens. Such compounds are named 3,9-dihydroxy-5,6-dihydro-benz[c]acridines. In this embodiment of the invention it is preferred that R^1 is halogen or fluorine substituted methyl.

Another embodiment of the invention is a compound having Formula I, wherein X is N, Y is $-C(R^2)-$, R^a is H and R^b is $'R^e$, having Formula V



Formula V

wherein,

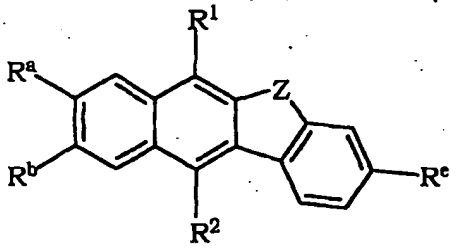
R^e and $'R^e$ are OH, optionally independently etherified or esterified;

Z is $-C(R^3,'R^3)-$ or $-C(R^4,'R^4)-C(R^5,'R^5)-$, wherein R^3, $'R^3$, R^4, $'R^4$, R^5, and $'R^5$, independently are H, (1C-4C)alkyl, (2C-4C)alkenyl or (3C-6C) cycloalkyl, which alkyl, alkenyl and cycloalkyl groups can optionally be substituted with one or more halogens;

R^2 is H, halogen, CN, optionally substituted aryl, (1C-4C)alkyl, (2C-4C)alkenyl, (2C-4C)alkynyl, (3C-6C)cycloalkyl, which alkyl, alkenyl, alkynyl and cycloalkyl groups can optionally be substituted with one or more halogens.

In this embodiment it is preferred that R^2 is halogen or fluorine substituted methyl and R^3, $'R^3$, R^4, $'R^4$, R^5, and $'R^5$, independently are H or methyl. More preferred is that Z is $-C(R^4,'R^4)-C(R^5,'R^5)-$, wherein R^4, $'R^4$, R^5, and $'R^5$, are H.

Another embodiment of this invention is a compound according to formula I, wherein X is $-C(R^1)-$, Y is $-C(R^2)-$, having Formula VI



Formula VI

wherein,

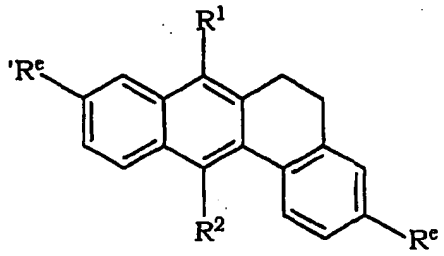
one of R^a or R^b is $'R^e$;

R^e and $'R^e$ are OH, optionally independently etherified or esterified;

R^1 and R^2 independently are H, halogen, CN, optionally substituted aryl, (1C-4C)alkyl, (2C-4C)alkenyl, (2C-4C)alkynyl or (3C-6C)cycloalkyl, which alkyl, alkenyl, alkynyl and cycloalkyl groups can optionally be substituted with one or more halogens;

Z is $-C(R^3,'R^3)-$ or $-C(R^4,'R^4)-C(R^5,'R^5)-$, wherein R^3, $'R^3$, R^4, $'R^4$, R^5, and $'R^5$, independently are H, (1C-4C)alkyl, (2C-4C)alkenyl or (3C-6C) cycloalkyl, which alkyl, alkenyl and cycloalkyl groups can optionally be substituted with one or more halogens. In this embodiment it is preferred that R^1 or R^2 is halogen or fluorine substituted methyl.

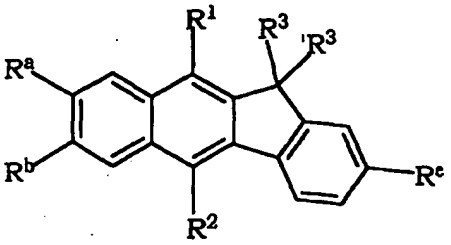
Also preferred in this embodiment are those compounds according to Formula VI whereby R^a is $'R^e$; R^b is H; Z is $-C(R^4,'R^4)-C(R^5,'R^5)-$, wherein R^4, $'R^4$, R^5, and $'R^5$ are H, which compounds are having Formula VII



Formula VII

wherein,
R^e and $'R^e$ are OH, optionally independently etherified or esterified;
R^1 and R^2 independently are H, halogen, CN, optionally substituted aryl, (1C-4C)alkyl, (2C-4C)alkenyl, (2C-4C)alkynyl or (3C-6C)cycloalkyl, which alkyl, alkenyl, alkynyl and cycloalkyl groups can optionally be substituted with one or more halogens, whereby it is preferred that R^1 is halogen or methyl, optionally fluorine substituted, and R^2 is hydrogen, which compounds are named 5,6-dihydro-3,9-dihydroxy-benz[*a*]anthracenes;

or compounds according to formula VI, whereby Z is $-C(R^3,'R^3)-$, having Formula VIII



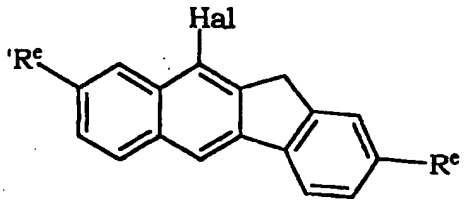
Formula VIII

wherein,
one of R^a or R^b is $'R^e$;
R^1 and R^2 independently are H, halogen, CN, optionally substituted aryl, (1C-4C)alkyl, (2C-4C)alkenyl, (2C-4C)alkynyl or (3C-6C)cycloalkyl, which alkyl, alkenyl, alkynyl and cycloalkyl groups can optionally be substituted with one or more halogens, whereby it is preferred that R^1 is halogen or methyl, optionally substituted with fluorine, and R^2 is hydrogen;
R^3 and $'R^3$ independently are H or CH^3, which compounds are named 11H-2-hydroxy-benzo[*b*]fluorenes.

In view of high selectivity for the ERβ, more preferred compounds are compounds according to formula VIII, wherein R^a is $'R^e$, R^b is H, R^3, $'R^3$ are H or methyl, R^1 or R^2 is H and the other of R^1 or R^2 is halogen, CN, optionally substituted aryl, (1C-4C)alkyl, (2C-4C)alkenyl, (2C-4C)alkynyl or (3C-6C)cycloalkyl, which alkyl, alkenyl, alkynyl and cycloalkyl groups

can optionally be substituted with one or more halogens, whereby it is preferred to select for R^1 or R^2 halogen or methyl, optionally substituted with fluorine. In general it is preferred that R^3 and $'R^3$ are H.

The best mode of the invention, in view of selectivity for the ERβ, is a compound according to Formula IX



Formula IX

wherein,
R^e and $'R^e$ are OH, optionally independently etherified or esterified;
Hal is fluorine, chlorine, bromine or fluorinated methyl, whereby from these possibilities for Hal the chlorine is most preferred.

The ester and ether compounds in the collection of compounds according to the invention aften have activity as prodrug. Preferred ester and ether prodrugs are carboxylic acid esters or alkyl ethers on one or both hydroxyl groups, and more preferred prodrugs are (2C-6C)carboxylic acid esters, such as esters of (iso)butanoic acid, or (1C-4C) alkyl ethers.
A prodrug is defined as being a compound which converts in the body of a recipient to a compound as defined by the formulas I to IX. Notably, the hydroxy groups as depicted in the formulas above can for example be substituted by alkyl*oxy, alkenyl*oxy, acyl*oxy, aroyloxy, alk*oxycarbonyloxy, sulfonyl groups or phosphate groups, whereby the carbon chain length of the groups denoted with an asterisk (*) is not considered to be sharply delimited, while aroyl generally will comprise a phenyl, pyridinyl or pyrimidyl, which groups can have substitutions customary in the art, such as alkyl*oxy, hydroxy, halogen, nitro, cyano, and (mono-, or dialkyl*-)amino. The length of the alkyl, alkenyl and acyl groups is selected depending on the desired properties of the prodrugs, whereby the longer chained prodrugs with for example lauryl or caproyl chains are more suitable for sustained release and depot preparations. It

is known that such substituents spontaneously hydrolyse or are enzymatically hydrolysed to the free hydroxyl substituents on the skeleton of the compound. Such prodrugs will have biological activity comparable to the compounds to which they are converted in the body of the recipients. The active compound to which a prodrug is converted is called the parent compound. The onset of action and duration of action as well as the distribution in the body of a prodrug may differ from such properties of the parent compound.

Substitution variants of the compounds of the present invention are possible for similar use. A substitution variant is defined to be a compound which comprises in its molecular structure the structure as defined by the formula I. The skilled person inspecting the group of compounds provided by the present invention will immediately understand that modification by a substituent to the skeleton can yield a compound with similar biological activity as the compound without this particular substituent. It is common practise in the art to test such substitution variants for the expected biological activity so that it is a routine skill to obtain useful substitution variants of compounds according to the invention.

Other terms used in this description have the following meaning:

alkyl is a branched or unbranched alkyl group, for example methyl, ethyl, propyl, isopropyl, butyl, sec-butyl, tert-butyl, hexyl, octyl, capryl, or lauryl;

alkenyl is a branched or unbranched alkenyl group, such as ethenyl, 2-butenyl, etc.;

alkynyl is a branched or unbranched alkynyl group, such as ethynyl and propynyl.

halogen refers to fluorine, chlorine, bromine and iodine;

aryl is a mono- or polycyclic, homo- or heterocyclic aromatic ring system, such as phenyl, naphtyl or pyridinyl; a monocyclic ring with 6 atoms is preferred for use;

aroyl is arylcarbonyl such as a benzoyl group;

alkanoyl means an oxo-substituted alkyl group, such as 2-oxobutyl or an acyl group;

acyl is an alkylcarbonyl group.

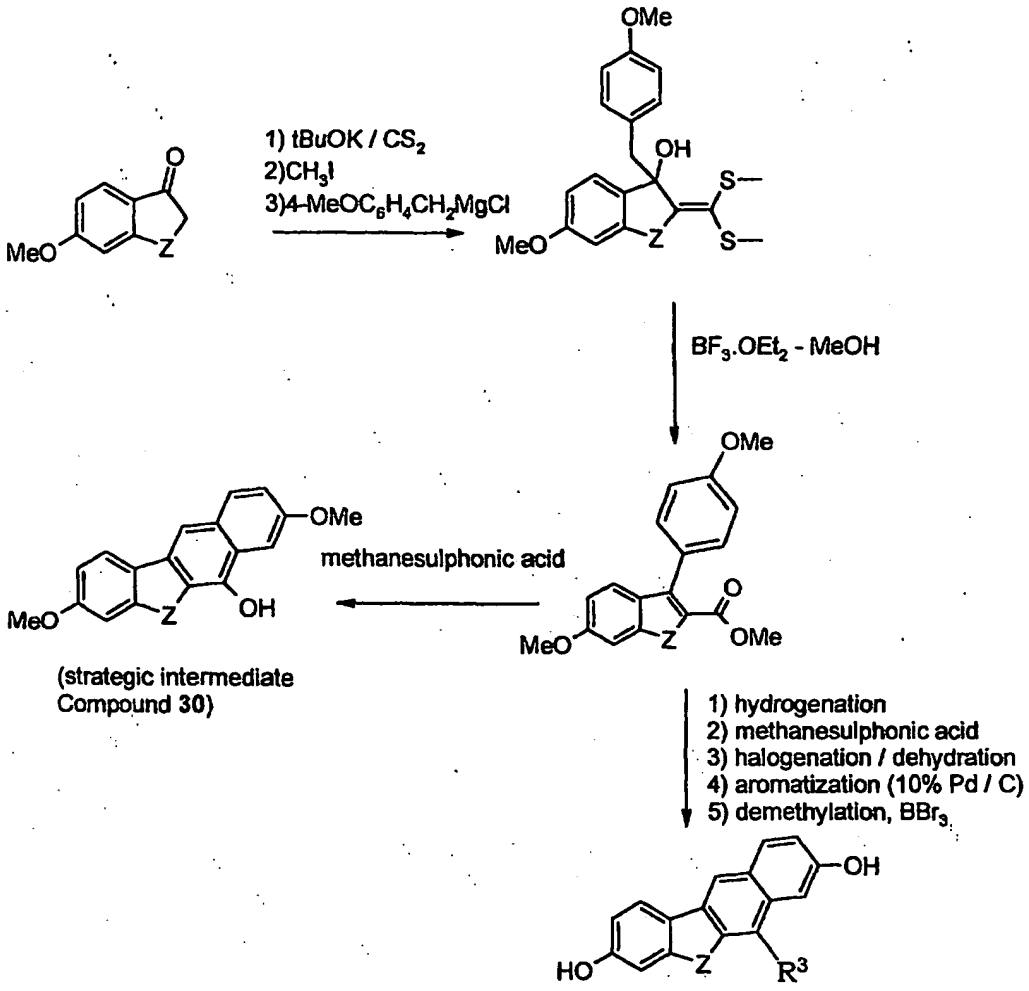
The prefixes (1C-4C), (2C-4C) etc. have the usual meaning to restrict the meaning of the indicated group to those with 1 to 4, 2 to 4 etc. carbon atoms.

The estrogen-receptor affinity profile of the compounds according to the present invention, makes them suitable as improved estrogens or anti-estrogens, in the sense that they can be used for estrogen-receptor related medical treatments, such as those for contraception or for treatment or prevention of benign prostate hypertrophy, cardiovascular disorders, menopausal complaints, osteoporosis, estrogen dependent tumour control or central nervous system disorders such as depression or Alzheimer's disease.

In particular those compounds which have selective affinity for the ERβ receptor are suitable for estrogen-receptor related medical treatments under diminished estrogen-related side-effects. This is most desirable when these compounds are used in the treatment of osteoporosis, cardiovascular disorders and central nervous system disorders such as depression or Alzheimer's disease.

The compounds of the invention can be produced by various methods known in the art of organic chemistry in general. More specifically the routes of synthesis as illustrated in the schemes and examples can be used. A general description of the synthesis of halogenated benzo[b]fluorenes is depicted in scheme 1.

Scheme 1. General procedure to prepare benzofluorenes
Abbreviations used in the scheme are: tBu is tertiairy butyl, Me is methyl and Et is ethyl; R^3 is a halogen originating from the halogenation step; Z can have any meaning as defined for Formula I.



The intermediate for further substitutions (strategic intermediate; e.g. compound **30** in examples 9, 10 and 11) can be made from its precursor in scheme 1 by adding methanesulphonic acid to the precursor and warming (about 60 °C) for some time (about 30 minutes).

Ester prodrugs can be made by esterification of compounds with free hydroxyl groups by reaction with appropriate acyl chlorides in pyridine.

The present invention also relates to a pharmaceutical composition comprising the non-steroidal compound according to the invention mixed with a pharmaceutically acceptable auxiliary, such as described in the standard reference Gennaro et al., Remmington's Pharmaceutical Sciences, (18th ed., Mack publishing Company, 1990, see especially Part

8: Pharmaceutical Preparations and Their Manufacture.). The mixture of the compounds according to the invention and the pharmaceutically acceptable auxiliary may be compressed into solid dosage units, such as pills, tablets, or be processed into capsules or suppositories. By means of pharmaceutically suitable liquids the compounds can also be applied as an injection preparation in the form of a solution, suspension, emulsion, or as a spray, e.g. nasal spray. For making dosage units, e.g. tablets, the use of conventional additives such as fillers, colorants. polymeric binders and the like is contemplated. In general any pharmaceutically acceptable additive which does not interfere with the function of the active compounds can be used. The compounds of the invention may also be included in an implant, a vaginal ring, a patch, a gel, and any other preparation for sustained release.

Suitable carriers with which the compositions can be administered include lactose, starch, cellulose derivatives and the like, or mixtures thereof used in suitable amounts.

Furthermore, the invention relates to the use of the non-steroidal compound according to the invention for the manufacture of a medicament for estrogen-receptor related treatments and treatment of estrogen-receptor related disorders such as peri- and/or post-menopausal complaints. Thus the invention also pertains to the medical indications of peri- and/or post-menopausal (climacteric) complaints and osteoporosis, i.e. a method of treatment in the field of hormone replacement therapy (HRT), comprising the administration to a patient, being a woman, of a compound as described hereinbefore (in a suitable pharmaceutical dosage form).

Further, the invention relates to the use of the non-steroidal compound according to the invention in the manufacture of a medicament having contraceptive activity. Thus the invention also pertains to the medical indication of contraception, i.e. a method of contraception comprising the administration to a subject, being a woman or a female animal, of a progestogen and an estrogen as is customary in the field, wherein the estrogen is a compound as described hereinbefore (in a suitable pharmaceutical dosage form).

Finally the invention relates to the use of the non-steroidal compound for the manufacture of a medicament having selective estrogenic activity, such a medicament being generally suitable in the area of HRT (hormone replacement therapy).

The dosage amounts of the present compounds will be of the normal order for estrogenic compounds, e.g. of the order of 0.01 to 100 mg per administration.

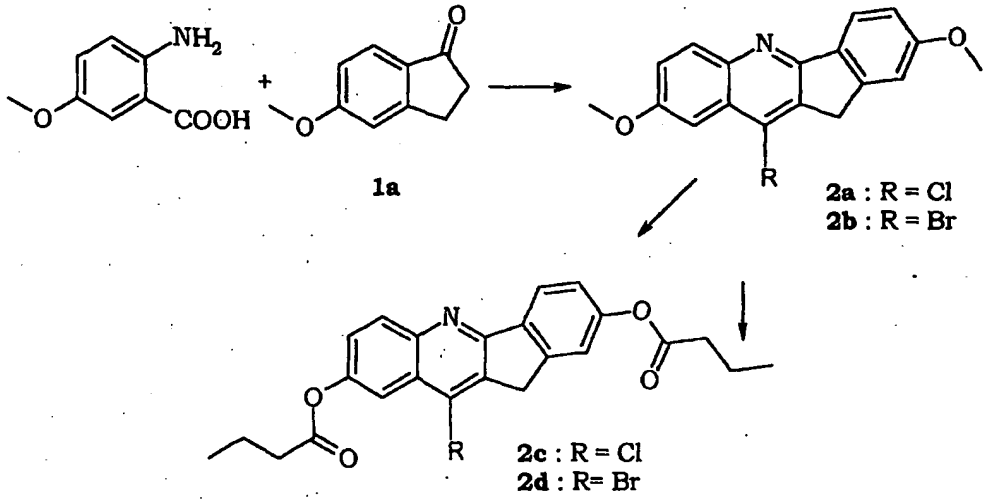
The invention is further illustrated hereinafter with reference to some unlimitative examples and the corresponding formula schemes referred to.

EXAMPLES

In the examples the compounds are identified with numbers, for example **1a**, **1b**, **2** etc.. These numbers refer to the definitions of the compounds in the schemes.

Example 1

Scheme 2. Synthesis of specified indenoquinolines:



Example 1a

10-chloro-2,8-dimethoxy-11*H*-indeno[1,2-*b*]quinoline: **2a**

Guided by the procedure of Yamato *et al* [*J. Med. Chem.* **32** (1989) 1295-1300] a mixture of 5-methoxy-anthranilic acid (2.0 mmol) and 5-methoxy-indan-1-one **1a** (2.4 mmol) was heated for 1 hour at 170° and 2 hours at 200°C. The resulting precipitate was collected and washed successively with pyridine and ether.

The solid material was taken up in $POCl_3$ (6 ml) and refluxed for 2 hours. The reaction was poured into ice water and neutralized with ammonia. The solid material was filtered off, washed with water and dried *in vacuo*. 80 µmol of the solid and 0.5 g pyridine hydrochloride were heated at 200°C for 1-1.5 hours, The reaction mixture was cooled to room temperature and taken up in $NaHCO_3$(aq) and extracted with ethyl acetate.

Purification by chromatography on silica gel (dichloromethane/methanol or toluene/acetone) afforded pure **2a** in 37% yield.(Rf = 0.47 toluene/acetone (3:2)); ESI-MS : M+H = 284, M-H = 282.

Example 1b

10-bromo-2,8-dimethoxy-11*H*-indeno[1,2-*b*]quinoline: **2b**

Compound **2b** was prepared in 11% yield, in the same fashion as described for the preparation of **2a**, but using $POBr_3$ (2.5 g) instead of $POCl_3$ (Rf = 0.47 toluene/acetone (3:2)); ESI-MS : M+H = 328 + 330 (1:1).

Example 1c

dibutyryl ester of 10-chloro-2,8-dihydroxy-1*H*-indeno[1,2-*b*]quinoline: **2c**

Compound **2a** (13 µmol) was treated with n-butyryl chloride (10 µl) in pyridine (1 ml) for 2 hours. The mixture was poured into water, extracted with ethyl acetate and concentrated. SiO_2-chromatography of the residue gave pure **2c** in 45% yield. (Rf = 0.67 heptane/ethyl acetate (3:2)); ESI-MS : M+H = 424.2.

Example 1d

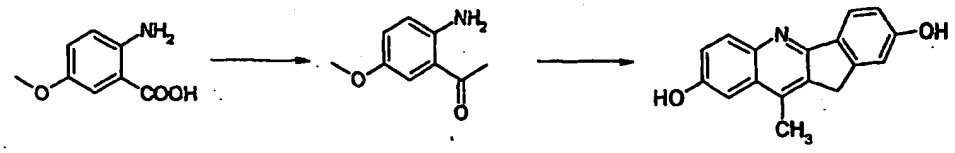
dibutyryl ester of 10-bromo-2,8-dihydroxy-11*H*-indeno[1,2-*b*]quinoline: **2d**

Compound **2b** (42 µmol) was treated with n-butyryl chloride (30 µl) in pyridine (2 ml) for 15 hours. The mixture was poured into water, extracted with ethyl acetate and concentrated. SiO_2-chromatography of the residue gave pure **2d** in 49% yield. (Rf = 0.63 heptane/ethyl acetate (3:2)); ESI-MS : M+H = 468.0 + 470.0 (1:1).

Example 2

10-methyl-2,8-dihydroxy-11*H*-indeno[1,2-*b*]quinoline: **4**

Scheme 3



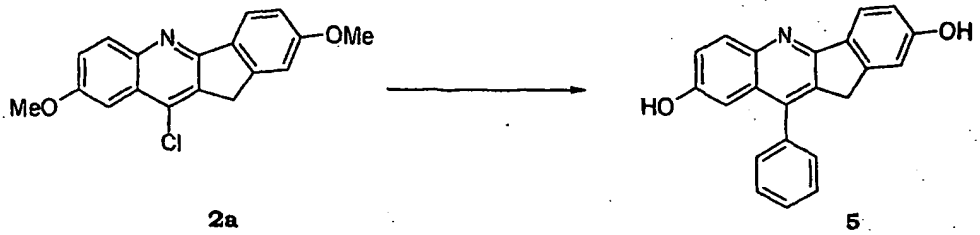
3 **4**

Compound **4** was synthesized following the procedure described by Czarny *et al* [*Heterocycles*, (1997) 2089-2092]. Anthranilic acid (2.0 mmol) in THF (10 ml) was treated with methyllithium 1.6M in ether (6.0 mmol) at -20°C and was allowed to warm to room temperature over 2 hours. The mixture was poured into NH_4Cl (aq), extracted with ethyl acetate and dried. Purification of the residue by SiO_2-chromatography (heptane/ethyl acetate) gave pure 2-amino-5-methoxy-acetophenone **3** in 44% yield. Compound **3** (0.6 mmol) was condensed with 5 methoxy indanone (0.8 mmol) in acetic acid (3 ml) and 3 drops of sulfuric acid at 115°C for 3 hours. After cooling to room temperature the precipitate was filtered off, washed with acetic acid and dried in vacuo. The solid material was taken up in 1.5 ml CH_2Cl_2 and BBr_3 (0.23 mmol) was added. After 2 hours the mixture was carefully poured into saturated $NaHCO_3$(aq) and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated. Purification on silica (toluene/ethyl acetate) afforded pure **4** in 54% yield. (Rf = 0.29 toluene/acetone (3:2)); ESI-MS : M+H = 264.0.

Example 3

10-phenyl-2,8-dihydroxy-11*H*-indeno[1,2-*b*]quinoline: **5**

Scheme 4



2a **5**

2,8-Dimethoxy-10-phenyl indeno-quinoline **5** was prepared following the procedure of Ali *et al* [*Tetrahedron*, **48** (1992) 8117-8126]. **2e** (160 µmol), phenylboric acid (25 mg), Na_2CO_3(aq) (180 µl 2M), $Pd(PPh_3)_4$ (6mg) and ethanol (55 µl) in toluene (2 ml) were refluxed for 48 hours. The reaction mixture was poured into water, extracted (CH_2Cl_2) and dried. The residue was taken up in ethylene diamine (1ml) and CH_2Cl_2 (0.5 ml) and stirred at 80°C for 1 hour. The mixture was acidified (2N HCl), extracted (CH_2Cl_2) and dried. SiO_2-chromatography (heptane/ethyl acetate) of the residue gave pure 10-phenyl indeno-quinoline. Demethylation with pyridine hydrochloride at 200°C, followed by chromatography on silica gel (dichloromethane/methanol) afforded pure **5** in 44% yield.(Rf = 0.29 dichloromethane /methanol (9:1)):ESI-MS : M+H = 326.2, M-H = 324.0.

Example 4

General procedure A: condensation of 5-methoxy-anthranilic acid with a keton, such as compound **1a**, **1b**, **1c**, **1d** or **1e** in schemes 5-8, and subsequent chlorination.

Guided by the procedure of Yamato *et al* [*J. Med. Chem.* **32** (1989) 1295-1300] a mixture of 5-methoxy-anthranilic acid (2.0 mmol) and a keton **1a** – **1e** (2.4 mmol) was heated for 1 hour at 170° and 2 hours at 200°C. The resulting precipitate was collected and washed successively with pyridine and ether.

The solid material was taken up in $POCl_3$ (6 ml) and refluxed for 2 hours. The reaction was poured into ice water and neutralized with ammonia. The solid material was filtered off, washed with water and dried *in vacuo*.

General procedure B: demethylation with pyridine hydrochloride.

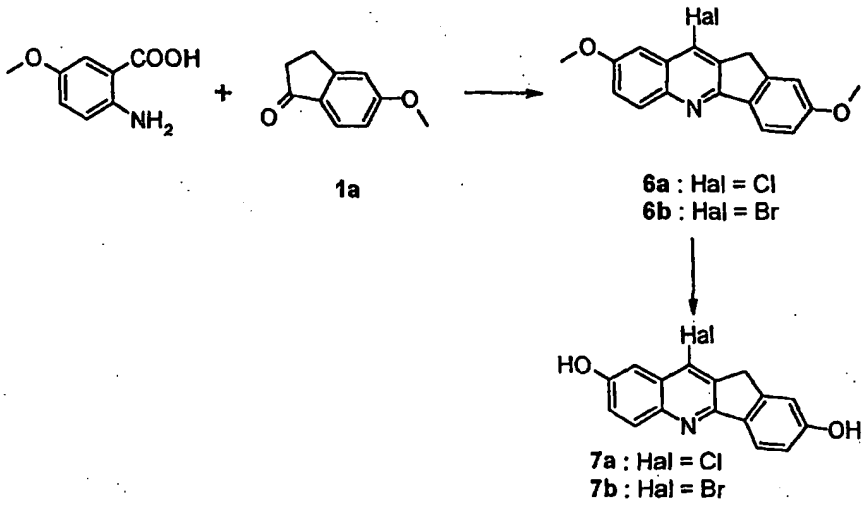
70 µmol of the compound to be demethylated and 500 mg pyridinium chloride were heated at 200°C for 1.5 hours, after which the cooled mixture was taken up in $NaHCO_3$(aq) and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by SiO_2-chromatography (dichloromethane/methanol or toluene/acetone).

General procedure C: demethylation with HBr.

70 µmol of the compound to be demethylated and 3 ml HBr (48% in water) were refluxed overnight, after which the cooled mixture was taken up in $NaHCO_3$(aq) and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated. The residue was purified by SiO_2-chromatography (toluene/acetone).

General procedure D: demethylation with BBr_3.
BBr_3 (0.53 mmol) was added to a solution of 0.18 mmol of the compound to be demethylated in 2 ml dry CH_2Cl_2 and the resulting mixture was stirred at roomtemperature for 1 hour. The mixture was carefully poured into sat. $NaHCO_3$ (aq) and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated. Purification by SiO_2-chromatography (toluene/ethyl acetate or toluene/acetone).

Scheme 5



1a

6a : Hal = Cl
6b : Hal = Br

7a : Hal = Cl
7b : Hal = Br

Example 4a

10-chloro-2,8-dihydroxy-11*H*-indeno[1,2-*b*]quinoline: **7a**

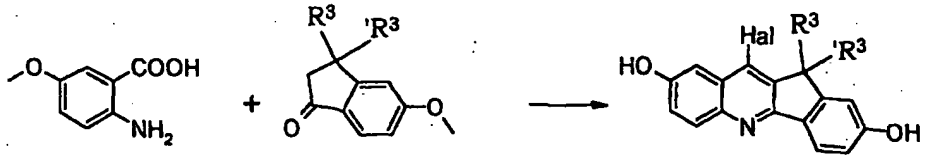
5-methoxy-anthranilic acid and 5-methoxy-indan-1-one were condensed using general procedure **A** to give **6a** in 44% (Rf = 0.57 heptane/ethyl acetate (3:2)); ESI-MS : M+H = 312.0. **6a** was demethylated using to procedure **C** to give **7a** in 84% yield. (Rf = 0.47 toluene/acetone (3:2)); ESI-MS : M+H = 284, M-H = 282.

Example 4b

10-bromo-2,8-dihydroxy-11*H*-indeno[1,2-*b*]quinoline: **7b**

5-methoxy-anthranilic acid and 5-methoxy-indan-1-one **1a** were condensed following general procedure **A** using $POBr_3$ instead of $POCl_3$ to give **6b** in 67% (Rf = 0.55 heptane/ethyl acetate (3:2)); ESI-MS : M+H = 355 + 357 (1:1). **6b** was demethylated using general procedure **B** to give **7b** in 16% (Rf = 0.47 toluene/acetone (3:2)); ESI-MS : M+H = 328 + 330 (1:1).

Scheme 6



1b : R^3=Me, $'R^3$=H
1c : R^3=$'R^3$=Me

7c : R^3=Me, $'R^3$=H, Hal=Cl
7d : R^3=R^3=Me, Hal=Cl

Example 4c

10-chloro-1-methyl-2,8-dihydroxy-11*H*-indeno[1,2-*b*]quinoline: **7c**

Compound **7c** was prepared by condensing 5-methoxy-anthranilic acid and 5-methoxy-3-methyl-indan-1-one **1b** using general procedure **A**, followed by demethylation using general procedure **B** to give **7c** in 27% (Rf = 0.19 toluene/acetone (3:2)); ESI-MS : M+H = 298.0, M-H = 296.0.

Example 4d

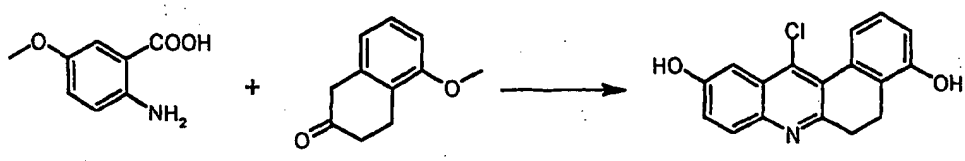
10-chloro-1,1-dimethyl-2,8-dihydroxy-11*H*-indeno[1,2-*b*]quinoline: **7d**

Compound **7d** was prepared by condensing 5-methoxy-anthranilic acid and 5-methoxy-3,3-dimethyl-indan-1-one **1c** using general procedure **A**, followed by demethylation using general procedure **B** to give **7d** in 2% (Rf = 0.30 toluene/acetone (3:2)); ESI-MS : M+H = 312.0, M-H = 310.0.

Example 4e

12-chloro-4,10-dihydroxy-5,6-dihydro-benz[*a*]acridine **8**

Scheme 7



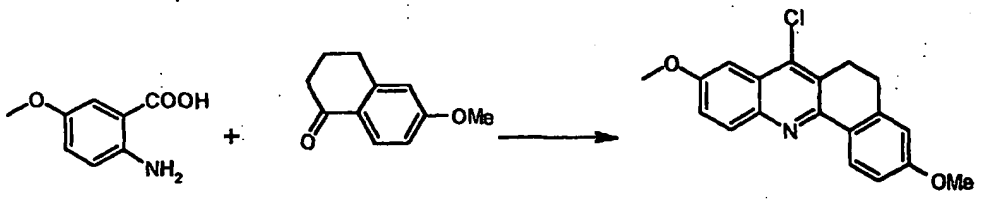
1d **8**

Compound **8** was prepared by condensing 5-methoxy-anthranilic acid and 5-methoxy-3,4-dihydro-1*H*-naphtalen-2-one **1d** using general procedure **A**, followed by demethylation using general procedure **D** to give **8** in 15% (Rf = 0.46 toluene/acetone (3:2)); ESI-MS : M+H = 298.0, M-H = 295.8.

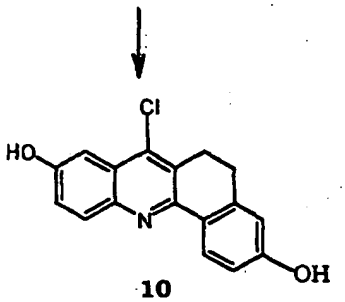
Example 4f

7-chloro-3,9-dihydroxy-5,6-dihydro-benz[c]acridine: **10**

Scheme 8



1 **1e** **9**



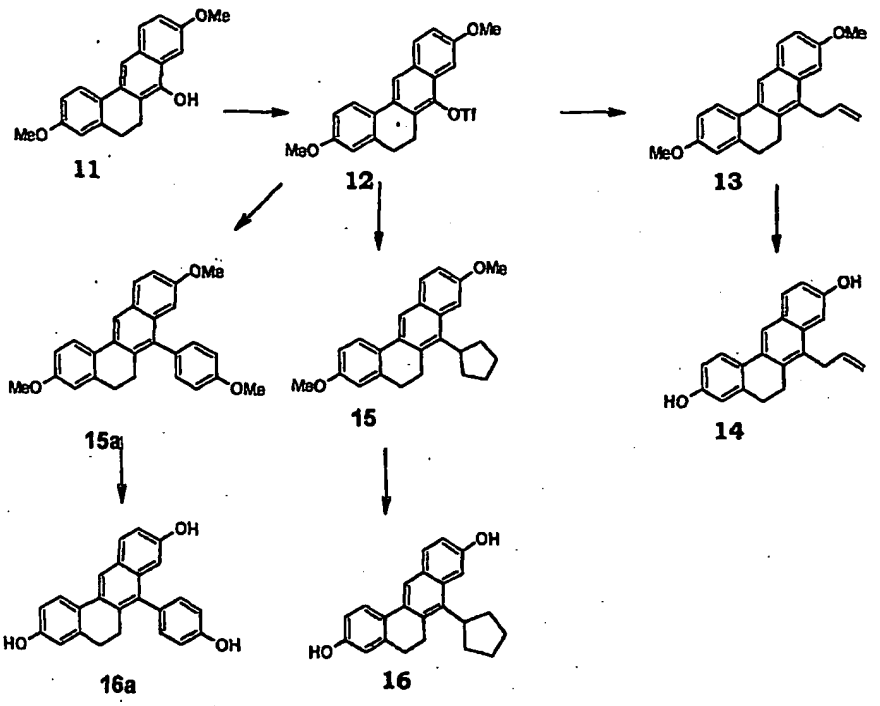
10

5-methoxy-anthranilic acid and 6-methoxy-3,4-dihydro-2*H*-naphtalen-1-one **1e** were condensed using general procedure **A** to give **9** in 61% (Rf = 0.67 heptane/ethyl acetate (3:2)); ESI-MS : M+H = 326.0. **9** was demethylated using general procedure **C** to give **10** in 73% yield. (Rf = 0.55 toluene/acetone (3:2)); ESI-MS : M+H = 298.0, M-H = 296.2.

Example 5

Scheme 9

Tf in the scheme means triflate



To 1 g of phenol **11** in in 15 ml of dry pyridine was added at O^0C, 0.66 ml of triflic anhydride. The mixture was stirred for 1 hr. Then ice water was added and the product extracted with ethyl acetate. The crude material was purified by chromatography (hept. / ethyl acetate) , to provide 1.38 g of **12** ; R_f 0.60 (hept. / ethyl acetate 7/3), NMR ($CDCl_3$) δ 2.87 and 3.10 (2x m, CH_2CH_2) , 3.87 and 3.95 (2x s, OCH_3), 8.03, 7.77, 7.30, 7.15, 6.89, 6.81 (7 aromatic protons).

A mixture consisting of 153 mg of LiCl, 32 mg of $PdCl_2(PPh_3)_2$, and 200 mg of **12** in 5 ml of DMF was stirred for 30 min at RT. Then 0.18 ml of allyltributyltin was added by syringe and the reaction was heated at reflux for 1 hr. After cooling to RT, water was added and the product was extracted with ethyl acetate. Chromatographic purification (hept / ethyl acetate) provided 190 mg of 3,9-dimethoxy-7-prop-2-enyl-5,6-dihydro-benz[a]anthracene, **13** ; R_f 0.61 (hept / ethyl acetate 7/3), NMR ($CDCl_3$) δ 2.86 and 3.02 (2x m, CH_2CH_2), 3.03 and 3.86 (2x s, OCH_3), 4.95-5.07 (4 m, allylic-CH_2), 6.02-6.13 (m, 1, allylic CH).

Deprotection of the methyl ethers was effected with sodium ethanethiolate. This was prepared from 0.46g 0f 50% sodiumhydride

dispersion (mineral oil) and 1.1 ml of ethanethiol in 8 ml of DMF at 0°C. After stirring this for 1/2 hr , a solution of 190 mg of **13** in 2 ml of DMF was added and the mixture was refluxed for 3 hr. The reaction was cooled diluted with water, acidified and extracted with ethyl acetate. Purification of the product thus isolated was effected by preparative HPLC to remove some cis and trans propenyl isomers, formed during the reaction. Thus 22 mg of crystalline 3,9-dihydroxy-7-prop-2-enyl-5,6-dihydro-benz[*a*]anthracene, **14**, was isolated , Mp 221-222 °C; R_f 0.22 (hept / ethyl acetate 7/3). NMR (DMSO) δ 2.70 and 2.89 (2x m, CH_2CH_2), 4.90-5.04 (4 m, allylic-CH_2), 5.98-6.08 (m, 1, allylic CH).

To a mixture of 250 mg of triflate **12** and 30 mg of NiCl2.DPPE in 11 ml of toluene was added 0.43 ml of a 2M-ether solution of cyclopentylmagnesium bromide. The reaction was heated during 1 hr at 60°C and then poured into sat.aq NH4Cl solution and extracted with ethyl acetate. Purification of the product was effected by chromatography (hept./ethyl acetate) to give 170 mg of **15**; R_f 0.47 (hept/ ethyl acetate 7/3); NMR ($CDCl_3$) δ 4.02, 2.22, 2.09, 1.89 (m, 9, cyclopentane), 2.82, 3.07 (m, 4, $CH2CH_2$), 3.86, 3.93 (s, 6, OCH_3).

A solution of 170 mg of **15** in 5 ml of methylenechloride was treated with 250 µl of BBr3. After stirring for 2 hr the reaction was complete. Ice was added and the product extracted with ethyl acetate. Purification was effected by chromatography over silica gel (toluene / ethyl acetate) as eluent, to give 45 mg of 3,9-dihydroxy-7-cyclopentyl-5,6-dihydro-benz[*a*]anthracene, **16**; Mp 233-235°C; NMR (DMSO) 3.91 (m, 1, CH) , 1.75-2.17 (m, 8, cyclopentane), 2.70, 2.97 (m, 2x m, 4, CH_2CH_2), 9.42, 9.58 (2xs, 2, OH).

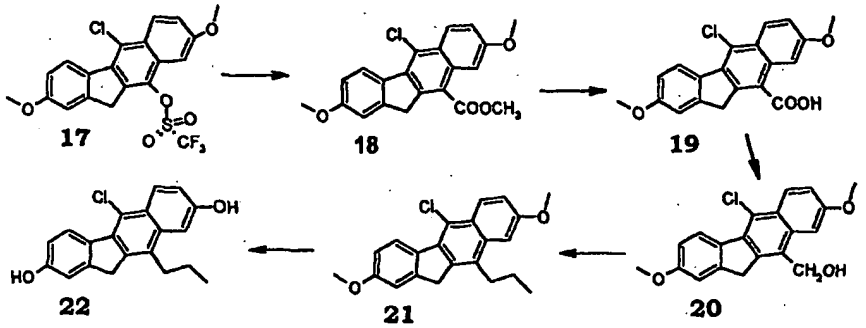
A mixture consisting of 200 mg of triflate (**12**) , 76 mg of p-methoxyphenylboronic acid, 26 mg of $Pd(PPh_3)_4$, 145 mg of K3PO4 in 3 ml of dioxane was heated for 5 hr at 90°C at an oil bath . The reaction was diluted with water and extracted with ethyl acetate. The organic material thus obtained was purified by chromatography (hept./ethyl acetate) and provided 162 mg of required 3,9-dimethoxy-7-(4-methoxyphenyl)-5,6-dihydro-benz[*a*]anthracene, **15a**; R_f 0.59 (hept./ ethyl acetate 7/3) R_f

triflate 0.62; NMR ($CDCl_3$) δ 2.70, 2.80 (2xm, 4, CH_2CH_2), 3.70, 3.85, 3.92 (3x s, 9, OCH_3).

To a solution of 162 mg of trimethoxy derivative **15a** in 5 ml of methylenechloride was added at –40°C 0.3 ml of BBr_3. The mixture was then stirred at ambient temperature for 3 hr. After pouring into ice water the product was extracted with ethyl acetate and the crude product thus obtained was purified by reversed phase chromatography (silica C18, acetonitrile-water as eluent), to provide 65 mg of crystalline 3,9-dihydroxy-7-(4-hydroxyphenyl)-5,6-dihydro-benz[*a*]anthracene, **16a**; Rf 0.48 (hept./ ethyl acetate 4/6) , Mp 272°C , NMR (DMSO)) δ 2.55 , 2.65 (2x m, 4, CH2CH2), 9.43, 9.45, 9.55 (3x s, 3, OH's).

Example 6

Scheme 10



A solution of 680 mg of triflate **17** in a mixture of 10 ml of DMF, 4 ml of methanol, 0.6 ml of triethyl amine, 2 ml of THFand 40 mg of 1,3-bis(diphenylphosphino)propane was flushed with nitrogen for 5 min and then purged with CO for 5 min. To the solution was then added 20 mg of $Pd(OAc)_2$ and the mixure was heated under CO atmosphere (balloon) for 4 hr at 60°C (an additional portion of catalyst system was added after 1.5 hr). Upon pouring the mixture in water, the products were extracted in ethyl acetate. After drying and concentration, the crude product was finally purified by chromatochraphy over silica gel. This gave 400 mg of **18**, Mp 157°C, Rf 0.40 (hept. / ethyl acetate 8/2), NMR ($CDCl_3$)δ 3.88, 3.96, 4.10 (3x s, 9, OCH_3), 4.25 (s, 2, CH_2).

A suspension of 400 mg of **18** in a mixture of 5 ml of dioxane, 2 ml of water and 150 mg of KOH was heated for 2 hr at 100 °C (The mixture

became readily a clear solution). The reaction was diluted with water and acidified with 2N HCl. The precipitates were filtered and dried in vacuo, to give 350 mg of carboxylic acid **19** ; Mp 269-270; Rf 0.40 (CH_2Cl_2 / methanol 9/1).

To a suspension of 150 mg of **19** in 3 ml of THF was added 0.5 ml of 10M borane.dimethylsulfide. A yellowish precipitate resulted . This was stirred at 45 °C for 1.5 hr. The reaction was carefully diluted with water and extracted with ethyl acetate. The crude product thus obtained was triturated with diisopropylether. This gave 110 mg of alcohol **20** as white solid; Mp 193°C; NMR (DMSO) 3.85 , 3.94 (2x s, 6, OCH_3), 4.19 (s, 2, CH_2) , 4.97 (m, 2, CH_2OH), 5.22 (m, 1, OH);. Rf 0.20 (hept / eth.acetate 6/4) .

A suspension of 560 mg of alcohol **20** in 4 ml of methylenechloride was treated with 60 mg of triphenylphosphine and then with 75 mg of 1,2-dibromo-1,1,2,2-tetrachloroethane. After stirring for 15 minutes the bromination was complete, and the reaction was worked up by dilution with water and extracion with ethylacetate. The residue which remained after washing , drying and concentration was disolved in 4ml of dry THF and added to a cuprate solution (prepared by addition of 300µl of 2.8M ethylmagnesium chloride in THF to a stirred suspension of 60 mg of CuBr and 30 mg of LiCl in in 2 ml of THF at –60 °C) . After removing of the cooling the mixture was slowly allowed to come to 0°C. Then the reaction was quenched by addition of sat aq. NH_4Cl solution and extracted with ethyl acetate. Chromatography provided 21 mg of 2,8-dimethoxy-5-chloro-10-propyl-11*H*-benzo[*b*]fluorene, **21**, as a white solid; Mp 143-145 Rf 0.62 (hept. / ethylac. 8/2); NMR ($CDCl_3$) δ 1.08 (s, 3, CH_3),1.78 (m, 2, CH_2), 3.07 (m, 2, CH_2) 3.90 and 3.97 (2x s, OCH_3), 4.03 (s, 2, CH_2).

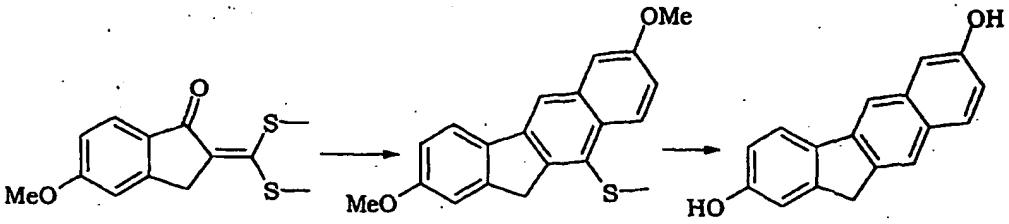
A solution of 20 mg of **21** in 1.5 ml of methylenechloride was treated with 100 µl of BBr3 at –50 °C. After stirring at ambient temperature for 2 hr the reaction was complete. Ice was added and the product extracted with ethyl acetate. The residue which remained after washing, drying and concentration of the organic phase was treated with a small amount of CH_2Cl_2-CCl_4 to provide 13 mg of essentially pure 2,8-dihydroxy-5-chloro-10-propyl-11*H*-benzo[*b*]fluorene, **22**, as a white solid; Mp 223-224; Rf 0.34

(hept. / eth. acetate 6/4) ; NMR (DMSO) δ 1.07 (s, 3, CH_3),1.68 (m, 2, CH_2), 2.87 (m, 2, CH_2), 4.02 (s, 2, CH_2), 9.72 and 9.87 (2x s, 2, OH's).

Example 6

2,7-dihydroxy-11*H*-benzo[*b*]fluorene: **25**

Scheme 11



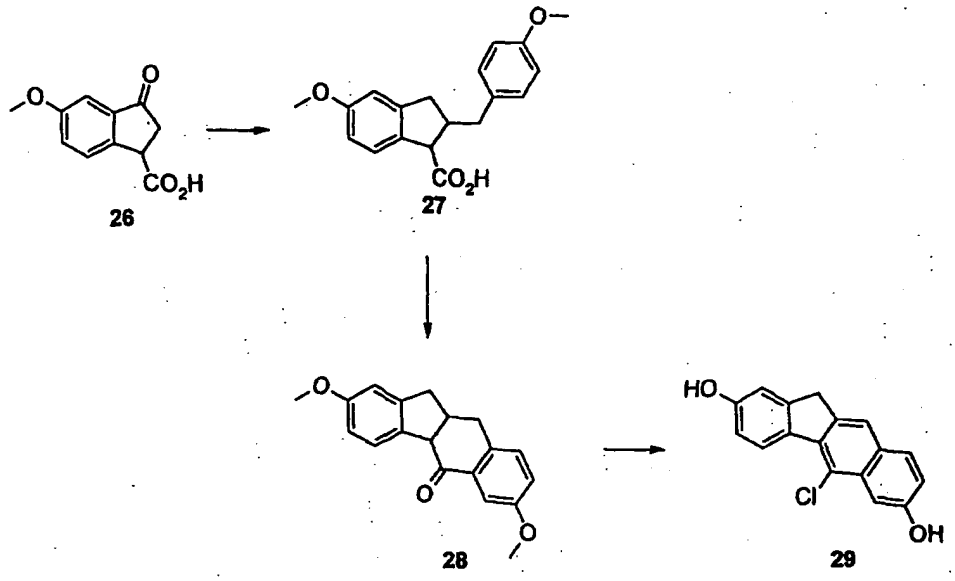
23 **24** **25**

11 ml 3-methoxybenzyl magnesiumchloride (1M in diethyl ether) was added to **23** (7.5 mmol) in 100 ml diethyl ether at 0°C and the reaction mixture was stirred for 1 hour at 20°C. The mixture was poured into sat. NH_4Cl(aq), extracted with ethyl acetate and dried over $MgSO_4$. After evaporation of the solvent the crude product was purified by chromatography (heptane/ethyl acetate) on silica gel. The pure fractions were combined and concentrated. The resulting product was taken up in 50 ml methanol and treated with $BF_3.Et_2O$ (21 mmol). After 15 minutes the temperature was raised to 60°C and 1 hour later the reaction mixture was poured into water, extracted with CH_2Cl_2 and the organic layer washed with $NaHCO_3$ (aq). The extract was dried over $MgSO_4$, concentrated and the residue was purified on silica gel (heptane/ethyl acetate) affording pure **24** in 34% yield.(Rf = 0.54 heptane/ethyl acetate (3:2)). A suspension of **24** (0.22 mmol) and Raney nickel (washed with ethanol, 1g) in 7 ml ethanol was stirred for 2 hours at 50°C. The Raney nickel was filtered off and the filtrate concentrated. The residue (0.08 mmol) was taken up in 1.5 ml CH_2Cl_2 and BBr_3 (0.23 mmol) was added. After 2 hours the mixture was carefully poured into sat. $NaHCO_3$(aq) and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated. Purification on silica (toluene/ethyl acetate) afforded pure **25** in 56% yield.(Rf = 0.40 toluene/ethyl acetate (4:1)); ESI-MS : M+H = 249.2, M-H = 247.0.

Example 8

2,7-dihydroxy-5-chloro-11*H*-benzo[*b*]fluorene: **29**

Scheme 12



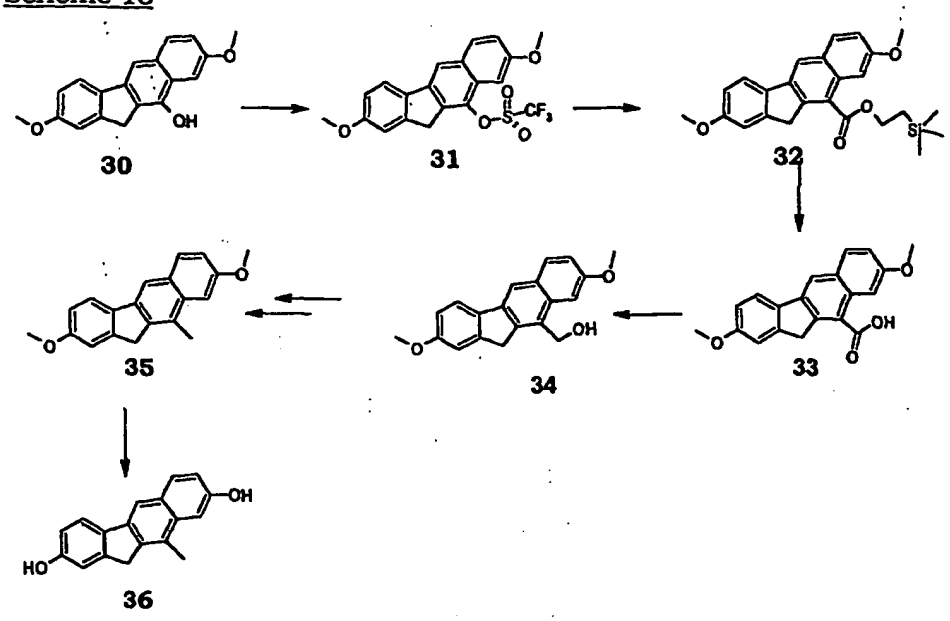
Compound **27** was prepared in 44% yield, in a similar manner as described for the preparation of compound **26**, but using 4-methoxybenzaldehyde instead of 3-methoxybenzaldehyde. (Rf = 0.45 toluene/acetone (4:1)); ESI-MS: M+H = 313.4, M-H = 311.0.

A mixture of **27** (2.8 mmol), TFA (5 ml) and TFAA (5ml) in CH_2Cl_2 (2 ml) was stirred for 2 hours at 50°C after which another 5 ml TFA and 5 ml TFAA were added. After 1 hour the mixture was poured into icewater and extracted with ethyl acetate. The organic layer was washed with water, sat. $NaHCO_3$ (aq) and brine. The organic extract was dried over $MgSO_4$ and concentrated. The residue was purified on silica gel (toluene/acetone) to give pure **28** in 56% yield. (Rf = 0.83 toluene/acetone (4:1)); ESI-MS: M+H = 295.2.

Compound 2,7-dihydroxy-5-chloro-11*H*-benzo[*b*]fluorene, **29**, was prepared in 5% yield in a similar manner as described for the preparation of compound **60** from **59** (See example 15a). (Rf = 0.72 toluene/ethyl acetate (3:2)); ESI-MS : M-H = 281.0.

Example 9

Scheme 13



A solution of 300 mg of triflate **31** in a mixture of 4 ml of DMF , 2 ml of 2-trimethylsilylethanol, 0.4 ml of triethyl amine , and 20 mg of 1,3-bis(diphenylphosphino)propane was flushed with nitrogen for 5 min and then purged with CO for 5 min. To the solution was then added 9 mg of $Pd(OAc)_2$ and the mixure was heated under CO atmosphere (balloon) for 2.5 hr at 70°C (an additional portion of catalyst system was added after 1.5 hr). Upon pouring the mixture in water, the products were extracted in ethyl acetate. After drying and concentration, the remainders of trimethylsilylethanol were removed at the vacuum pump. The product was finally obtained by chromatochraphy over silica gel. This gave 220 mg of **32**, solidifying on trituration with heptane; Mp 107-108°C ; NMR($CDCl_3$) δ 0.15 (s, 9, 3, $Si(CH_3)$) , 1.22 (m, 2, CH_2), 4.58 (m, 2, CH_2); 4.23 (s, 2, CH_2), 3.88, 3.95 (2 s, OCH_3). R_f 0.71 (tol/eth.ac 95/5) .

To a solution of 160 mg of the trimethylsilylethyl ester **32** in 5 ml of THF was added dropwise (!) 0.45 ml of 1 M solution of TBAF in THF. As soon as starting material had disappeared the mixture was quickly diluted with water and acidified with 1N HCl. The product was filtered and dried, to give 105 mg of almost pure carboxylic acid **33**, R_f 0.40 (methylenechl / methanol 9 / 1) ; NMR (DMSO) δ 3.83, 3.89 (2x s, OCH_3), 4. 21 (s, 2, CH_2).

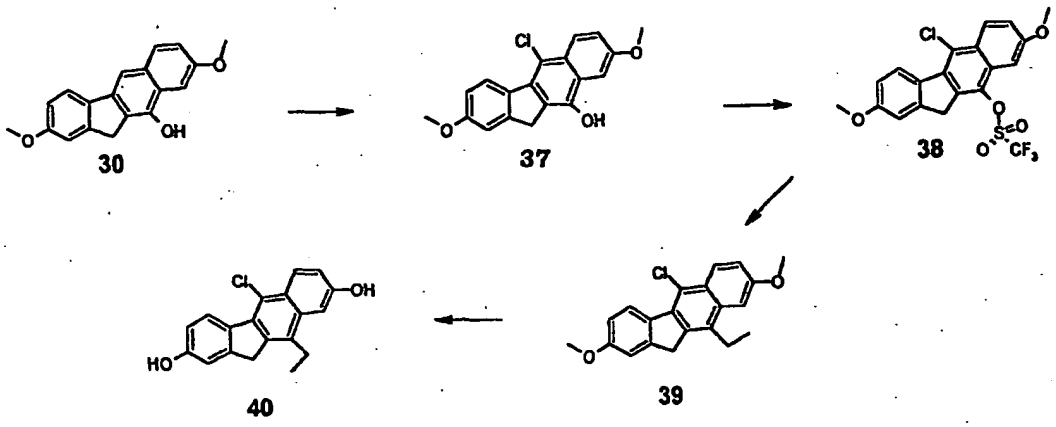
To a solution of 96 mg of carboxylic acid **33** in 3 ml of dry THF was added 150 µl of 10M BMS. After stirring for 4 hr the reduction was complete. The mixture was diluted with water, acidified with 2N HCl and stirred for ½ hr. The resulting alcohol **34** was isolated by filtration from the aquous phase and amounted 80 mg . R_f 0.26 (hept / eth.ac. 6/4), NMR($CDCl_3$) δ 3.83 and 3.87 (2xs, 6, OCH_3), 4.21 (s, 2, CH_2).

A suspension of 90 mg of alcohol **34** in 4 ml of methylenechloride was treated with 100 mg of triphenylphosphine and then with 130 mg of 1,2-dibromo-1,1,2,2-tetrachloroethane. After stirring for 15 minutes the bromination was complete, and the reaction was worked up by dilution with water and extracion with ethylacetate. The residue which remained after washing , drying and concentration was disolved in 4ml of dry THF and cooled to –45°C. Then 50 mg of $LiAlH_4$ was added, and then stirred for 20 min at 0°C. The reaction mixture was [poured into water and acidified with 2N HCl. The product was extracted with ethylacetate. Washing, drying and concentration provided 40 mg of essentially pure methyl derivative 2,8-dimethoxy-10-methyl-11*H*-benzo[*b*]fluorene, **35**; R_f 0.66 (hept / ethylac. 6/4); NMR ($CDCl_3$) δ 2.65 (s, 3, CH_3), 3.91 and 3.98 (2x s, OCH_3), 3.99 (s, 2, CH_2).

To a solution of 40 mg of **35** in 5 ml of methylenechloride was added at –25°C 200 µl BBr_3.
The mixture was then stirred at ambient temperature for 2 hr to completion of the reaction. The mixture was quenched by pouring into water and extraction of the product with ethylacetate. The material thus obtained was purified by passing through a short silica column (tol/ ethyl ac as eluent) and provided 22 mg of diol 2,8-dihydroxy-10-methyl-11*H*-benzo[*b*]fluorene, **36**; R_f 0.40 (tol / ethyl ac 7/3); Mp 265 °C; NMR (DMSO d-6) δ 9.48, 9.58 (2x s, OH) , 2.52 (s, 3, CH_3), 3.92 (s, 2, CH_2).

Example 10

Scheme 14



To a solution of 2.4 g of phenol **30** in 30 ml of DMF was added at rt in several smaller portions in about 5 min 2.7 g of 2,2,3,4,5,6-hexachlorocycloheha-3,5-dienone. After stirring for ½ h the reaction was complete and the mixture was poured into water and the product extracted with ethyl acetate. Purification af the product by chromatography provided 950 mg of p-chloroderivative **37** as a brown solid; Mp 165-166°C , R_f 0.38 (hept / ethylac. 6/4).

To a solution of 900 mg of chlorophenol **37** in 8 ml of pyridine was added at 0°C 700 µl of triflicanhydride. The mixture was stirred for an additional two hr at ambient temperature and then poured into water and extracted with ethyl acetate. The crude material was chromatographed over a short silica column , and the material thus obtained was treated with diisopropyl ether , to provide 800 mg of essentially pure triflate **38**, Mp 165-168°C, R_f 0.58 (hept / ethyl acetate 8/2) ; NMR($CDCl_3$) 19F, -73 ppm triflate , 1H NMR 3.90, 3.98 (2x s,OCH_3), 4.18 (s, 2, CH_2),

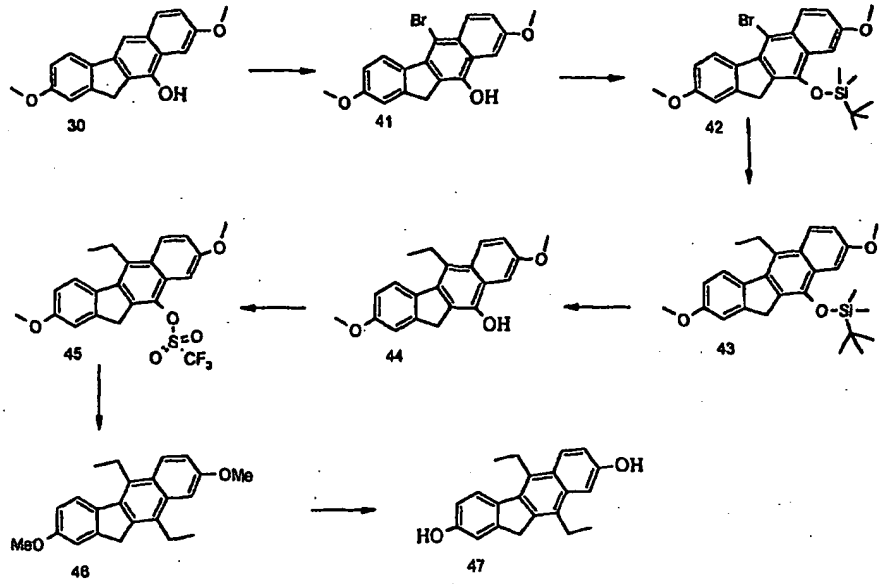
A solution of 70 mg of triflate **38** in 3 ml of toluene was charged with 10 mg of $NiCl_2$.DPPE, followed by 120 µl of 2.8M ethylmagnesiumchloride solution in THF). After stirring for two hour the reaction was complete. The materials were poured into 10%aq. NH_4Cl and extracted with ethyl acetate. After chromatography over silicagel 36 mg og ethyl derivative 2,8-dimethoxy-5-chloro-10-ethyl-11*H*-benzo[*b*]fluorene, **39**, remained as a white solid; Mp 163-165 °C; R_f 0.47 (hept / ethylac 8/2). NMR ($CDCl_3$) δ 1.35 (t, 3, CH_3), 3.10 (q, 2, CH_2), 4.02 (s, 2, CH_2), 3.90 , 3.98 (2x s, 6, OCH_3).

To a solution of 25 mg of **39** in 3 ml of methylenechloride was added at –25°C 100 µl BBr_3.

The mixture was then stirred at ambient temperature for 2 hr to completion of the reaction. The mixture was quenched by pouring into water and extraction of the product with ethylacetate. The material thus obtained was purified by passing through a short silica column (tol/ ethyl ac. as eluent) and provided 22 mg of diol 2,8-dihydroxy-5-chloro-10-ethyl-11*H*-benzo[*b*]fluorene, **40**; Rf 0.36 (hept / ethyl ac 6/4); Mp 250 - 251 °C; NMR (DMSO d-6) δ 9.75, 9.90(2x s, OH) , 1.25 (t, 3, CH_3), 3.00 (q, 2, CH_2) , 4.02 (s, 2, CH_2)

Example 11

Scheme 15



To a suspension of 1 gr of phenol **30** in 10 ml of acetonitrile was added in small portions at rt 600 mg of NBS. After 1 h the bromination was completed. The mixture was poured into water and the dark brown material was filtered, and triturated with 80%aq ethanol, to give after vacuo drying at 50°C 1.1 g of crude **41**.This was dissolved in 5 ml of DMF and 0.5 g of imidazole and 0.6 g of tBDMSCl were succesively added at 0°C. The reaction was stirred for 1 hr and then poured onto water and extracted with ether. The material thus obtained was purified by chromatography and triturated with 90% aq. ethanol to yield 1.1 g of

silylated product **42**; Mp 134-135°C; R_f 0.48 (hept / ethyl ac 9/1); NMR ($CDCl_3$) δ 0.28 (s, 2, $Si(CH_3)_2$)1.15 (s, 9,SitC_4H_9), 3.90 and 3.95 (2x s, 6, OCH_3). 4.00 (s, 2, CH_2).

To a mixture containing 200 mg of bromide **42**, and 30 mg of $NiCl_2$.DPPP in 5 ml of toluene under N_2atmosphere was added 300 µl of 2.8M ethylmagnesium chloride solution (inTHF)
After stirring for 2 hr the reaction was complete. The mixture was diluted with 10% aq. NH_4Cl solution and extracted with ethyl acetate. The crude material thus obtained was purified from the reduction product by silica gel chromatography, to give 55 mg of ethyl product **43** , Mp 118-120°C. ; R_f 0.50 (hept./ethyl acetate 9/1). NMR($CDCl_3$) δ 1.40 (t, 3, CH_3), 3.42 (q, 2, CH_2), 0.28 (s, 6, $Si(CH_3)_2$) , 1.18 (s, 9,Si tC_4H_9), 4.00 (s, 2, CH_2), 3.90 and 3.95 (2x s, 6, OCH_3).
Reduction product R_f 0.45 .

To 320 mg of silylether 14 in 3 ml of dry THF was added 1 ml of 1M TBAF in THF. .After stirring for 15 min the mixture was diluted with water and slightly acidified with 1N HCl. The product was extracted with ethyl acetate. After concentration of the organic phase the residue was treated with diisopropylether / heptane (1/1) to give 190 mg of a brownish solid phenol **44** ; R_f 0.29 (hept / ethyl acetate 7/3).
This matyerial was dissolved in 2 ml of pyridine and treated with 200 µl of triflic anhydride. After stirring for 1.5 h the reaction was complete . Ice water was added and the product extracted into ethylacetate. After chromatography 190 mg of triflate **45** were isolated ; Mp 199-200°C. R_f 0.67 (hept. / ethyl ac. 7/3);
NMR ($CDCl_3$) δ 1.42 (t, 3, CH_3), 3.47(q, 2, CH_2), 4.19 (s, 2, CH_2) ; -74 ppm ^{19}F resonance.

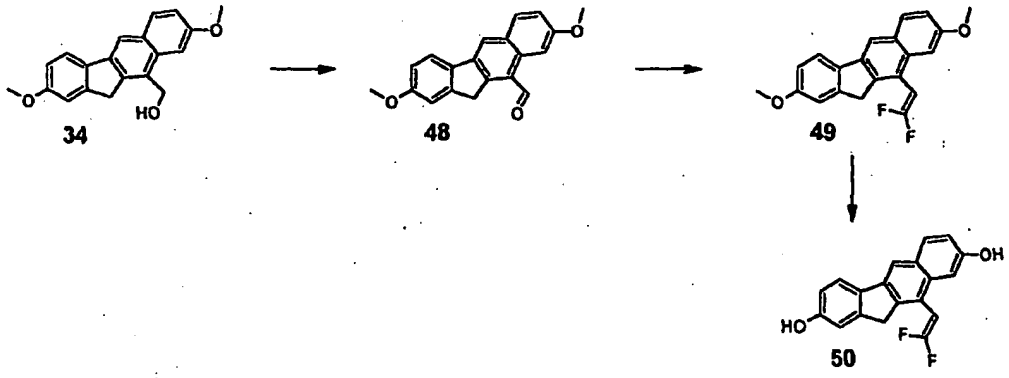
To a mixture containing 140 mg of triflate **45**, and 30 mg of $NiCl_2$.DPPP in 5 ml of toluene under N_2atmosphere was added 350 µl of 2.8M ethylmagnesium chloride solution (inTHF). The mixture was stirred for ½ hr at 45 °C . Then sat aq NH_4Cl was added and the products extracted with ethyl acetate. Chromatography provided 110 mg of 2,8-dimethoxy-5,10-diethyl-11*H*-benzo[*b*]fluorene, **46** ; Mp 155-157°C , R_f 0.46 (hept /

ethyl acetate 9/1) 0.46 . NMR ($CDCl_3$) δ 1.37 and 1.45 (2x t, 6, CH_3), 3.12 and 3.47(2x q, 4, CH_2), 4.01 (s, 2, CH_2).

To a solution of 100 mg of **46** in 3 ml of methylenechloride was added at -25°C 300 µl BBr_3.
The mixture was then stirred at ambient temperature for 1 hr to completion of the reaction. The mixture was quenched by pouring into water and extraction of the product with ethylacetate. The material thus obtained was purified treatment with hot ethyl acetate and provided 48 mg of diol 2,8-dihydroxy-5,10-diethyl-11*H*-benzo[*b*]fluorene, **47**; Rf 0.60 (tol / ethyl ac 7/3); Mp 255 °C (dec); NMR (DMSO d-6) δ 9.53, and9.59(2x s, OH) , 1.25and 1.30 (2x t, 3, CH_3), 3.00 and 3.37 (2x q, 2, CH_2) , 3.95 (s, 2, CH_2).

Example 12

Scheme 16



To a solution of 670 mg of alcohol **34** in 90 ml of methylenechloride was added 2,3 g of pyridiniumchlorochromate, 1.8 g of sodiumacetate and 4 g of silicagel. The mixture was stirred for 3 hr until completion of the reaction. The mixture was then filtered over Celite and concentrated , and the residue purified by filtration over silicagel (hept. / ethyl acetate) to give 600 mg of aldehyde **48** . NMR ($CDCl_3$) δ 10.95 (s, 1, CHO), 3.92, 4.00 (2x s, OCH_3) , 4.40 (s, 2, CH_2). Rf 0..56 (hept / ethyl acetate 6/4).

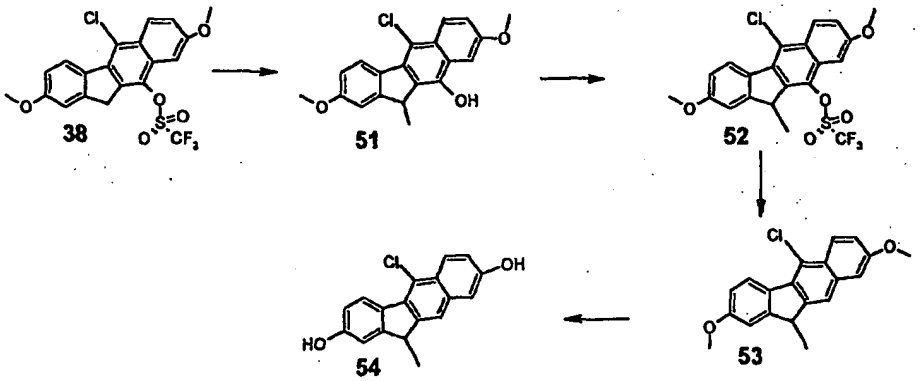
A solution of lithiumdiisoprpylamide was prepared by addition of 0.3 ml of 1.6M BuLi-heptane to 0.73 µl of diisopropylamine in 3 ml of dry THF at -60°C. To this solution was then added 133 mg of diphenyldifluoromethylphosphinoxde in 3 ml of THF. After stirring for 30

min. at -60°C a solution of 100 mg of aldehyde **48** in 2 ml of THF was added and the cooling device was removed and the mixture was then stirred for an additional 3 hr at ambient temperature. The reaction was quenched by addition of water, followed by extraction of the product with ethylacetate. After passing through a silica column (hept / ethyl acetate as eluent) 90 mg of 2,8-dimethoxy-10-(2,2-difluoro-ethenyl)-11*H*-benzo[*b*]fluorene, **49**, was obtained; Mp 82-85°C; R_f 0.63 (hept / ethyl acetate 7/3) . NMR (CDCl3) δ 5.70 (d, $CHCF_2$), 3.97 (s,2,CH_2) , 3.90 ,and 3.97 (2x s, OCH_3).

To a solution of 60 mg of **49** in 4 ml of methylenechloride was added at -20°C 100 µl of BBr_3. The mixture was then stirred at ambient temperature for 3 hr, until completion of the reaction. Then ice water was added followed by extraction of the product with ethyl acetate. After passing through a short silica column (hept./ ethyl acetate as eluent) the purified material was treated with 90% ethanol , to give 35 mg of 2,8-dihydroxy-10-(2,2-difluoro-ethenyl)-11*H*-benzo[*b*]fluorene, **50**, Mp 211-212°C, R_f 0.16 (hept. / ethy ac. 6/4). NMR (DMSO d6) 9.55 and 9.72 (2xs, 2, OH), 6.12 (d, 1, $CHCF_2$), ^{19}F NMR -82 and -86 ppm, fluoro resonances.

Example 13

Scheme 17



To a mixture containing 200 mg of triflate **38**, and 30 mg of $NiCl_2$.DPPE in 5 ml of toluene under N_2atmosphere was added 350 µl of 2.8M methylmagnesium chloride solution (inTHF)

After stirring for 2 hr at 50°C the reaction was complete. The mixture was diluted with 10% aq. NH_4Cl solution and extracted with ethyl acetate. The crude material thus obtained was purified by silica gel chromatography, to

give 100 mg of product **51** , as a dark foam ; Rf 0.420 (hept./ethyl acetate 6/4). NMR (DMSO) δ 9.65 (s, 1, OH), 4.28 (m, 1, CH) 3.85, 3.92 (2x s, 6, OCH_3), 1.52 (d, 3, CH_3).

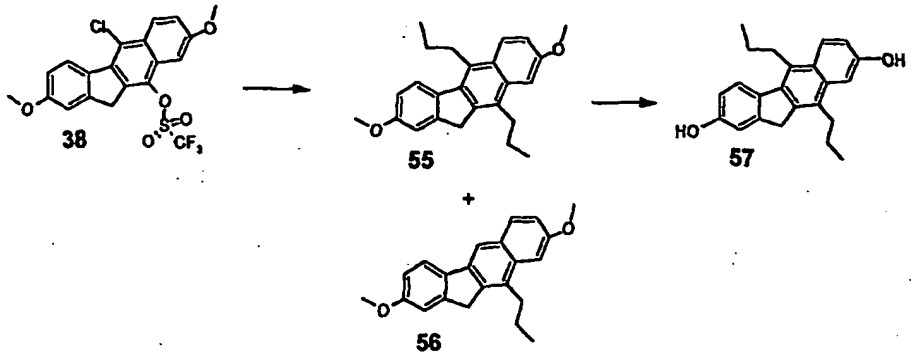
To a solution of 60 mg of chlorophenol **51** in 1 ml of pyridine was added at 0°C 100 µl of triflicanhydride. The mixture was stirred for an additional two hr at ambient temperature and then poured into water and extracted with ethyl acetate. The crude material was chromatographed over a short silica column , and the material thus obtained was treated with diisopropyl ether , to provide 52 mg of essentially pure triflate **52**, Mp 149-150°C, Rf 0.66 (hept / ethyl acetate 8/2) ; NMR 19F, ($CDCl_3$) –74 ppm triflate , NMR ($CDCl_3$) δ 3.91, 3.97 (2x s,6, OCH_3), 4.48 (m, 1, CH), 1.62 (d, 3, CH_3).

To a mixture containing 50 mg of triflate **52**, and 10 mg of $NiCl_2$.DPPE in 2 ml of toluene under N_2atmosphere was added 150 µl of 2.8M ethylmagnesium chloride solution (inTHF)
After stirring for 1/2 hr at 50°C the reaction was complete. The mixture was diluted with 10% aq. NH_4Cl solution and extracted with ethyl acetate. The crude material thus obtained was purified by silica gel chromatography, to give 23 mg of 2,8-dimethoxy-5-chloro-11-methyl-11*H*-benzo[*b*]fluorene, **53** ; Rf 0.47 (hept./ethyl acetate 8/2). NMR($CDCl_3$) δ 4.10 (m, 1, CH) 3.90, 3.95 (2x s, 6, OCH_3), 1.59 (d, 3, CH_3).

To a solution of 21 mg of **53** in 1.4 ml of methylenechloride was added at -20°C 100 µl of BBr_3. The mixture was then stirred at ambient temperature for 1 hr, until completion of the reaction. Then ice water was added followed by extraction of the product with ethyl acetate. After passing through a short silica column (tol./ ethyl acetate as eluent) the purified material was treated with ethanol / water , to give 12 mg of 2,8-dihydroxy-5-chloro-11-methyl-11*H*-benzo[*b*]fluorene, **54**, Mp 215-220°C, Rf 0.45 (tol. / ethy ac. 7/3). NMR (DMSO d6) 9.78 and 9.90 (2xs, 2, OH), 4.05 (m, 1, CH), 1.50 (d, 3, CH_3).

Example 14

Scheme 18



Triflate **38** (240 mg) was mixed with 6 ml of dry toluene and 50 mg of NiCl2.DPPE complex and flushed with nitrogen. Then 1 ml of a solution of 2M propylmagnesiumchloride –ether was added and stirring continued for 2 hr, until disappearance of the starting material. The mixture was then poured into sat. NH_4Cl solution and extracted with ethyl acetate. The products 2,8-dimethoxy-5,10-dipropyl-11*H*-benzo[*b*]fluorene, **55**, and 2,8-dimethoxy-10-propyl-11*H*-benzo[*b*]fluorene, **56**, thus obtained were saparated by chromatography (heptane / ethylacetate 98/2 as eluent), to provide 70 mg of dipropyl derivative **55** as well as 65 mg of monopropyl derivative **56**; Mp (**55**) 145-147°C , Mp (**56**) 130-132°C.

R_f (**55**) 0.65 (heptane/ ethylacetate 8/2) ; R_f (**56**) 0.60.

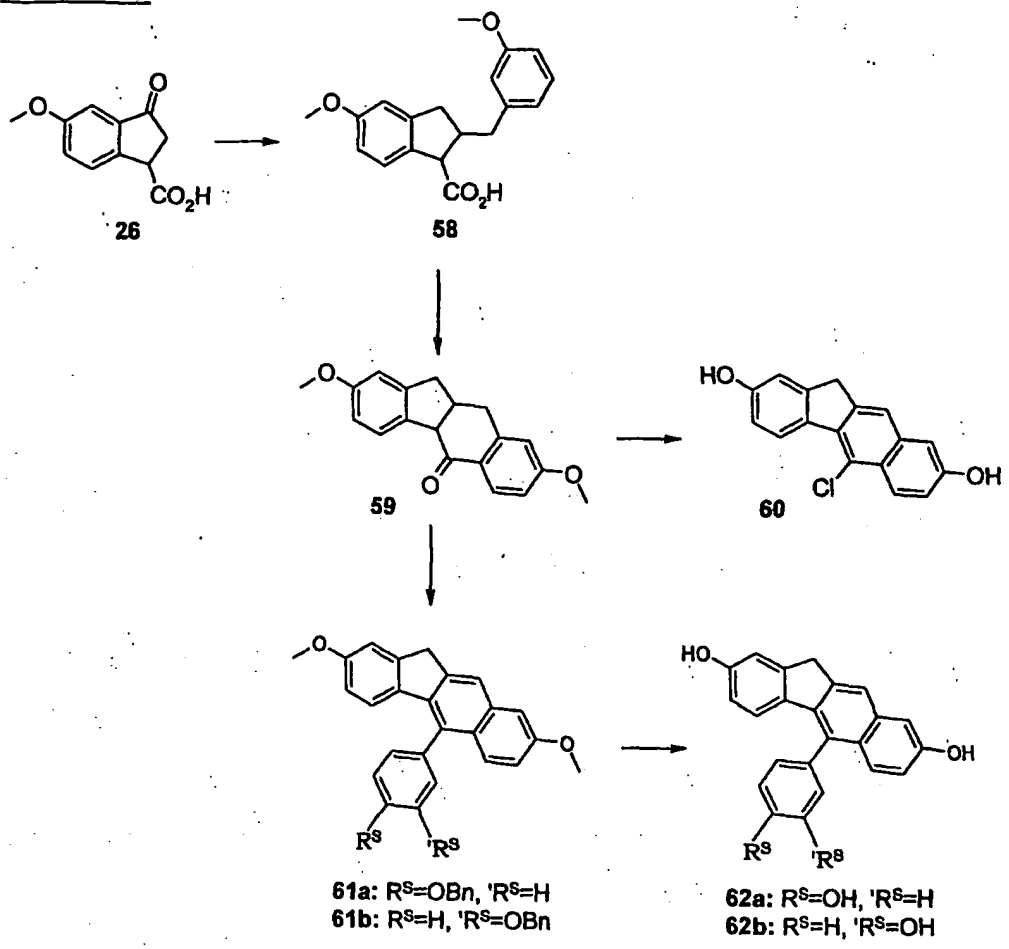
NMR ($CDCl_3$) δ (**55**) 1.10 and 1.21 (2xt, 6, CH_3), 1.80 (m,4, 2x CH_2), 3.07 and 3.39 (2xm, 4, CH_2), 3.90 and 3.97 (2x s, 6, OCH_3), 4.01 (s, 2, CH_2).

NMR($CDCl_3$) δ (**56**) 1.08 (t, 3, CH_3), 1.80 and 3.10 (2x m, 4, CH_2) , 3.89 and 3.97 (2x s, 6, OCH_3), 3.99 (s, 2, CH_2).

To a solution of 65 mg of **55** in 4 ml of methylenechloride was added at -20°C 250 µl of BBr_3. The mixture was then stirred at ambient temperature for 2 hr, until completion of the reaction. Then ice water was added followed by extraction of the product with ethyl acetate. The product which remained after washing , drying and concentration was triturated with diisopropylether to give 35 mg of white solid 2,8-dihydroxy-5,10-dipropyl-11*H*-benzo[*b*]fluorene, **57**; R_f 0.47 (hept. / ethyl acetate 6/4); Mp. 250 °C; NMR (DMSO) 1.05 and 1.15 (2x t, 6, CH_3) , 1.66 (m, 4, 2x CH_2), 2.94 and 3.28 (2x m, 4, CH_2), 3.93 (s, 2, CH_2), 9.56 and 9.53 (2xs, 2, OH's).

Example 15

Scheme 19



Example 15a

2,8-dihydroxy-5-chloro-11*H*-benzo[*b*]fluorene: **60**

A mixture of **26** [Chiu, C.K-F. et al, Aust. J. Chem., **45**, 1, 227-248 (1992)] (46 mmol), KOtBu (98 mmol) and 3-methoxybenzaldehyde (68 mmol) in 200 ml methanol was stirred at 50°C. After 2 hours water was added and the mixture was acidified with 2 N HCl. The solid was collected by filtration and recristallised from toluene/heptane.

A mixture of these crystals and palladium on charcoal (10% w/w, 3 g) in 800 ml ethyl acetate/methanol (3:1) was stirred under 30 psi of hydrogen for 5.5 hours. The catalyst was removed by filtration and the filtrate was concentrated to give **58** in 93% yield. (Rf = 0.49 toluene/acetone (4:1)), ESI-MS: M-H = 311.

A solution of **58** (40 mmol) in 250 ml methanesulfonic acid was stirred overnight at RT, poured into ice water and extracted with CH_2Cl_2. The organic extract was washed with sat. $NaHCO_3$(aq), dried over $MgSO_4$ and concentrated. Chromatography on silica gel (toluene/ethyl acetate) gave pure **59** in 62% yield. (Rf = 0.80 toluene/acetone (4:1)).

To a solution of **59** (0.19 mmol) in toluene (2.5 ml) was added PCl_5 (1.3 mmol). After stirring the mixture for 1 hour at 20°C it was poured into water and extracted with toluene. The organic layer was washed with sat. $NaHCO_3$ (aq), dried over $MgSO_4$, concentrated and purified on silica gel (heptane/ethyl acetate). The purified product was dissolved in CH_2Cl_2 (2 ml) and BBr_3 (0.4 mmol) was added. After 2 hours the mixture was carefully poured into sat. $NaHCO_3$ (aq) and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated. Purification on silica gel (toluene/ ethyl acetate) afforded pure **60** in 53% yield. (Rf = 0.26 toluene/ethyl acetate (4:1)); ESI-MS: M+H = 283.0, M-H = 281.0.

Example 15b

2,8-dihydroxy-5-(4-hydroxyphenyl)-11*H*-benzo[*b*]fluorene: **62a**

4-(Benzyloxy) phenyl lithium (1 mmol) (prepared from 4-(benzyloxy) phenyl bromide and butyl lithium at –30°C) was added to **59** (0.68 mmol) in THF (4 ml) at –30°C and the temperature was raised to RT over 1 hour. The mixture was poured into sat. NH_4Cl (aq), extracted with ethyl acetate, dried over $MgSO_4$ and concentrated. The residue was taken up in acetone (20 ml), p-toluenesulfonic acid (29 mg) was added and the mixture was stirred overnight at RT. Water was added and the mixture was extracted with ethyl acetate. The organic extract wa washed with sat. $NaHCO_3$ (aq), dried over $MgSO_4$ and concentrated. Purification on silica gel (heptane/ethyl acetate) afforded pure 2,8-dimethoxy-5-(4-benzyloxyphenyl)-11*H*-benzo[*b*]fluorene, **61a**, in 18% yield. (Rf = 0.61 heptane/ethyl acetate (4:1)); ESI-MS: M+H = 461.2.

A mixture of **61a** (0.11 mmol) and palladium on charcoal (10% w/w, 100 mg) in m-xylene (5 ml) was heated at 125°C for 1 hour. After the mixture had cooled ethanol (20 ml) was added and the mixture was stirred under an atmosphere of hydrogen for 1 hour. The catalyst was removed by filtration, the filtrate was concentrated and purified by chromatography on silica gel (toluene/ethyl acetate). The purified product was dissolved in CH_2Cl_2 and boron trifluoride-methyl sulfide complex (0.86 mmol) was added. The mixture was stirred

overnight at RT, poured into sat. $NaHCO_3$ (aq) and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated. Purification on silica (CH_2Cl_2/methanol) afforded pure **62a** in 40% yield. (Rf = 0.25 CH_2Cl_2/methanol (9:1)); ESI-MS: M-H = 339.0.

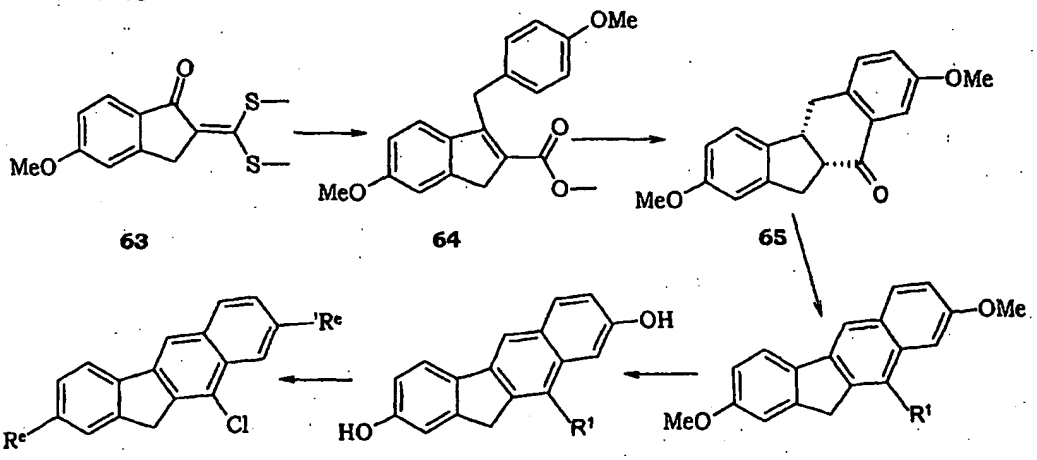
Example 15c

2,8-dihydroxy-5-(3-hydroxyphenyl)-11H-benzo[b]fluorene: **62b**

Compound **62b** was prepared from 2,8-dimethoxy-5-(3-benzyloxyphenyl)-11*H*-benzo[*b*]fluorene, **61b**, in 14% yield, in the same fashion as described for the preparation of **62a**, but using 3-(benzyloxy) phenyl lithium instead of 4-(benzyloxy) phenyl lithium (Rf = 0.26 CH_2Cl_2/methanol (9:1)); ESI-MS: M+H = 341.2, M-H = 339.0.

Example 16

Scheme 20



68a : R^e='R^e=$OC(O)C(CH_3)_3$
68b : R^e='R^e=$OC(O)C_3H_7$
68c : R^e=$OC(O)C_3H_7$, 'R^e=OH
68d : R^e=OH, 'R^e=$OC(O)C_3H_7$

67a : R^1 = Cl
67b : R^1 = Br
67c : R^1 = I
67d : R^1 = Me
67e : R^1 = CF_3

66a : R^1 = Cl
66b : R^1 = Br
66c : R^1 = I
66d : R^1 = Me
66e : R^1 = CF_3

Example 16a

2,8-dihydroxy-10-chloro-11*H*-benzo[*b*]fluorene: **67a**

59 ml 4-methoxybenzyl-magnesium chloride (0.2 M in diethyl ether) was added to **63** [J.V. Ram and M. Nath, *Indian J. Chem. Sect.B*; **34**, 416-422 (1995)] (11.6 mmol) in 70 ml THF at 0°C and the reaction mixture was stirred for 0.5 hour at 20°C. The mixture was poured into saturated aq.

NH_4Cl, extracted with diethyl ether and dried over $MgSO_4$. After evaporation of the solvent the crude product was purified by chromatography on silica gel (heptane/ethyl acetate). The pure fractions were concentrated and the material obtained was taken up in 95 ml methanol and treated with $BF_3.Et_2O$ (28 mmol). After 0.5 hour the temperature was raised to 65°C and after 0.5 hour the reaction mixture was poured into water, extracted with CH_2Cl_2 and the organic layer washed with $NaHCO_3$ (aq). The extract was dried over $MgSO_4$, concentrated and the residue was recrystallised from methanol to afford pure **64** in 45% yield (Rf = 0.48 heptane/ethyl acetate (3:2)).

A mixture of **64** (5 mmol) and palladium on carbon (10% Pd (w/w), 300 mg) in 120 ml ethanol/acetic acid (5:1) was stirred under an atmosphere of hydrogen for 1 hour. The catalyst was removed by filtration and the filtrate was concentrated.

The residue was dissolved in methanesulfonic acid and stirred at 90°C for 15 minutes after which the mixture was poured into ice water and extracted with ethyl acetate. The organic layer was washed with $NaHCO_3$(aq) and dried over $MgSO_4$. Chromatography on silica gel (heptane/ethyl acetate) gave pure **65** in 85% yield. (Rf = 0.49 heptane/ethyl acetate (2:1))

To a solution of **65** (0.8 mmol) in toluene (8 ml) was added PCl_5 (4.8 mmol). After stirring the mixture for 2 hours at 20°C it was poured into ice water and extracted with toluene. The organic layer was washed with $NaHCO_3$ (aq), dried over $MgSO_4$ and concentrated. The residue was dissolved in 12 ml m-xylene/toluene (2:1) palladium on carbon (10% w/w, 200 mg) was added and the mixture was refluxed for 2 hours. The catalyst was filtered off and the filtrate was concentrated. Chromatography (heptane/ethyl acetate) gave pure 2,8-dimethoxy-10-chloro-11*H*-benzo[*b*]fluorene **66a** in 92% yield. (Rf = 0.58 heptane/toluene (1:1))

BBr_3 (3.5 mmol) was added to a solution of **66a** (1.18 mmol) in 30 ml CH_2Cl_2 and after 1 hour another 2.1 mmol of BBr_3 was added. After 1.5 hours the mixture was carefully poured into sat. $NaHCO_3$ (aq) and extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated. Purification on silica (toluene/ethyl acetate) afforded pure **67a** in 87% yield. (Rf = 0.38 toluene/ethyl acetate (4:1)); ESI-MS: M+H = 283.0, M-H = 281.2.

Example 16b

2,8-dihydroxy-10-bromo-11*H*-benzo[*b*]fluorene: **67b**

A mixture of 500 mg $POBr_3$ and 0.34 mmol **65** was heated for 1 hour at 90°C and 1 hour at 120°C after which the mixture was poured into water and extracted with ethyl acetate. The organic layer was washed with sat. $NaHCO_3$(aq), dried over $MgSO_4$ and concentrated. The residue was purified on silica gel (heptane/ethyl acetate). The resulting bromide was treated with 100 mg palladium on carbon (10% w/w) in 2 ml m-xylene at 125°C for 2 hours. The catalyst was removed by filtration and the filtrate concentrated to give pure 2,8-dimethoxy-10-bromo-11*H*-benzo[*b*]fluorene, **66b**, in19% yield. (Rf = 0.50 heptane/toluene (1:1)). Compound **67b** was obtained in 92% yield in the same fashion as described for the conversion of **66a** to **67a**. (Rf = 0.52 toluene/ethyl acetate (7:3)); ESI-MS: M-H = 325.0 + 327.0 (1:1).

Example 16c

2,8-dihydroxy-10-iodo-11*H*-benzo[*b*]fluorene: **67c**

65 (0.34 mmol) was dissolved in ethanol and 1 ml hydrazine monohydrate was added. After 4 hours refluxing, water was added and the hydrazone was extracted with CH_2Cl_2. The organic layer was washed with water, dried and concentrated. The residue was taken up in 1.5 ml triethylamine and 0.2 g iodine in 0.7 ml THF was added at 0°C. After 1 hour the reaction mixture was diluted with toluene, poured into ice water and extracted with toluene. The organic layer was washed with 1N HCl and saturated $NaHCO_3$(aq), dried over $MgSO_4$ and concentrated. The residue was dissolved in 8 ml m-xylene/toluene (2:1) palladium on carbon (10% w/w, 100 mg) was added and the mixture was heated at 125°C for 2 hours. After cooling the catalyst was filtered off, the filtrate was concentrated and the residue was purified on silica (heptane/ethyl acetate) to give pure 2,8-dimethoxy-10-iodo-11*H*-benzo[*b*]fluorene: **66c** in 41% yield. (Rf = 0.58 (heptane/ethyl acetate (4:1)).

66c was demethylated in a similar manner as described for the conversion of **66a** to **67a** to give pure **67c** in 62% yield. (Rf = 0.50 toluene/ethyl acetate (4:1)); ESI-MS : M+H = 375.2, M-H = 373.0.

Example 16d

2,8-dihydroxy-10-methyl-11*H*-benzo[*b*]fluorene: **67d**

65 (0.34 mmol) was dissolved in 5 ml dry diethyl ether and 0.13 ml methyl magnesium chloride (22%, w/w) in THF) was added . After 2 hours water was added and the mixture was extracted with diethyl ether. The organic layer was dried over $MgSO_4$, concentrated and the residue was purified on silica gel (toluene/ethyl acetate). The alcohol was taken up in 5 ml acetone and 4 mg p-toluenesulfonic acid was added. After 3 hours water was added and the mixture was extracted with ethyl acetate. The organic layer was washed with $NaHCO_3$(aq), dried over $MgSO_4$, concentrated and the residue was purified on silica gel (heptane/ethyl acetate). The purified product was treated with 20 mg palladium on carbon (10% w/w) in 3 ml m-xylene/toluene (2:1) at 125°C for 2 hours. The catalyst was removed by filtration and the filtrate was concentrated. The residue was chromatographed on silica gel (heptane/ethyl acetate) to give pure 2,8-dimethoxy-10-methyl-11*H*-benzo[*b*]fluorene, **66d**, in 15% yield. (Rf = 0.67 toluene/ethyl acetate (3:2)).

66d was demethylated in a similar manner as described for the conversion of **66a** to **66a** to give pure **67d** in 51% yield.(Rf = 0.22 toluene/ethyl acetate (3:2)).

Example 16e

2,8-dihydroxy-10-trifluoromethyl-11*H*-benzo[*b*]fluorene: **67e**

65 (0.51 mmol) was dissolved in 2 ml dry THF. Trifluoromethyl trimethylsilane (0.15 ml) was added and the mixture was cooled to -20°C. Tetrabutylammonium fluoride in THF (0.3 ml) was added and the temperature was raised to 0°C. After 2 hours another 0.35 ml Trifluoromethyl trimethylsilane was added at 0°C and the temperature was raised to 20°C. After 16 hours water was added and the mixture was extracted with ethyl acetate. The organic layer was concentrated and the residue was chromatographed on silica gel (toluene/ethyl acetate). The alcohol and 2 mg p-toluenesulfonic acid were taken up in 2 ml toluene and refluxed for 3 hours after which water was added. The mixture was extracted with toluene, the organic layer was concentrated and purified on silica gel (toluene/ethyl acetate). The purified product was treated with 20 mg palladium on carbon (10%, w/w) in 3 ml m-xylene at 125°C for 24 hours. The catalyst was removed by filtration and the filtrate concentrated to give pure 2,8-dimethoxy-10-trifluoromethyl-11*H*-benzo[*b*]fluorene, **66e**, in 9% yield. (Rf = 0.77 toluene/ethyl acetate (3:2)). **66e** was deprotected

in a similar manner as **66a** to give pure **67e** in 21% yield.(Rf = 0.32 toluene/ethyl acetate (7:3)).

Example 16f

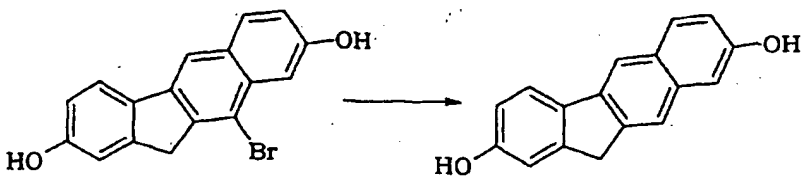
di-pivaloyl ester of 2,8-dihydroxy-10-chloro-11*H*-benzo[*b*]fluorene: **68a**
67a (1.8 mmol) was taken up in 15 ml of pyridine and pivaloyl chloride (5.4 mmol) was added. After 2 hours water was added and the white precipitate was collected by filtration. The precipitate was purified on silica gel (heptane/toluene) to give pure **68a** in 73% yield. (Rf = 0.81 (heptane/ethyl acetate (3:2); ^{1}H-NMR: δ = 1.40 ppm (s, 9H), 1.43 ppm (s, 9H), 4.01 ppm (s, 2H).

Example 16g

Mono and dibutyryl esters of 2,8-dihydroxy-10-chloro-11*H*-benzo[*b*]fluorene: **68b**, **68c** and **68d**
67a (1.0 mmol) was taken up in 22 ml of pyridine and butyryl chloride (1.0 mmol) was added. After 1 hour another 0.55 mmol of butyryl chloride was added. After another 1.5 hours water was added and the mixture was extracted with ethyl acetate. The organic layer was dried over $MgSO_4$ and concentrated. The residue was chromatographed on silica gel (heptane/ethyl acetate) to give pure **68b** in 51% yield (Rf = 0.68), **68c** in 14% yield (Rf = 0.43) and **68d** in 16% yield (Rf = 0.39 heptane/ethyl acetate (3:2)).

Example 17

2,8-dihydroxy-11*H*-benzo[*b*]fluorene: **69**
Scheme 21



67b **69**

A mixture of **67b** and palladium on carbon (10% w/w, 20 mg) in 2 ml ethanol was stirred under 25 psi of hydrogen for 7 hours. The catalyst was removed by filtration and the filtrate was concentrated. Purification on

silica gel (toluene/ethyl acetate) gave pure **69** in 22% yield. (Rf = 0.43 toluene/ethyl acetate (7:3)); ESI-MS : M+H = 159.2, M-H = 161.8.

Example 18

Compounds are tested for their estrogen receptor activity in a binding assay and in a transactivation assay.

Determination of competitive binding to cytoplasmic human estrogen receptor α or β from recombinant CHO cells is used to estimate the relative affinity (potency ratio) of a test compound for estrogen receptors present in the cytosol of recombinant Chinese hamster ovary (CHO) cells, stably transfected with the human estrogen receptor α (hERα) or β receptor (hERβ), as compared with estradiol (E_2).

The estrogenic and antiestrogenic activity of compounds is determined in an in vitro bioassay with recombinant Chinese hamster ovary (CHO) cells stably co-transfected with the human estrogen receptor α (hERα) or β receptor (hERβ), the rat oxytocin promoter (RO) and the luciferase reporter gene (LUC). The estrogenic activity (potency ratio) of a test compound to stimulate the transactivation of the enzyme luciferase mediated via the estrogen receptors hERα or hERβ is compared with the standard estrogen estradiol. The antiestrogenic activity (potency ratio) of a test compound to inhibit the transactivation of the enzyme luciferase mediated via the estrogen receptors hERα or hERβ by the estrogen estradiol is compared with the standard ICI 164.384 (= (7α,17ß)-N-butyl-3,17-dihydroxy-N-methylestra-1,3,5(10)-triene-7-undecanamide).

Results

Table 1

Compound	ERβ Transactivation	β/α ratio Transactivation	ERβ Binding
67a	+++	+++	+++
67b	+++	+++	+++
67c	+++	+++	+++
67d	+	++	++
67e	++	++	+++
69	+	+	++
25	+	-	++
68a	++	+++	Nd
68b	+++	+++	Nd
2a	++	+	++
2b	+	++	++
2c	++	++	Nd
2d	+	++	Nd
5	-	Nd	++
60	+++	+++	+++

Potency Transactivation (ERβ):

(% relative to 17β-estradiol)

- \- < 0.1%
- \+ between 0.1-4%
- ++ between 4-10%
- +++ >10%

β/α ratio Transactivation:

- \- < 3.5
- \+ between 3.5-10
- ++ between 10-30
- +++ >30
- *nd* = not determined

Potency Binding (ERβ):
(% relative to 17β-estradiol)
- <0.1%
+ between 0.1-2%
++ between 2-10%
+++ >10%
nd = not determined

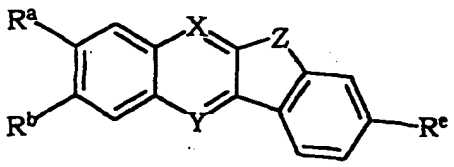
Table 2. Binding affinity of halogenated non-steroidal estrogens with ERα and ERβ

Compound	Binding ERα	Binding ERβ
7a	-	+++
7b	-	++
7c	+	++
7d	+++	+++
8	++	++
10	++++	++++
60	++	++++

Binding: *(% relative to 17β-estradiol)*
- < 0.3%
+ between 0.1-1.5%
++ between 1.5-3.5%
+++ between 3.5-8%
++++ >8%

Claims

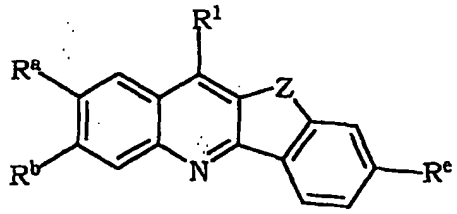
1. A compound having the formula I



Formula I

wherein,
one of R^a or R^b is $'R^e$;
R^e and $'R^e$ are OH, optionally independently etherified or esterified;
X is N or $-C(R^1)-$, wherein R^1 is H, halogen, CN, optionally substituted aryl, (1C-4C)alkyl, (2C-4C)alkenyl, (2C-4C)alkynyl or (3C-6C)cycloalkyl, which alkyl, alkenyl, alkynyl and cycloalkyl groups can optionally be substituted with one or more halogens;
Y is N or $-C(R^2)-$, with the proviso that X and Y are not both N, wherein R^2 has the same meaning as defined for R^1;
Z is $-C(R^3,'R^3)-$ or $-C(R^4,'R^4)-C(R^5,'R^5)-$, wherein R^3, $'R^3$, R^4, $'R^4$, R^5, and $'R^5$, independently are H, (1C-4C)alkyl, (2C-4C)alkenyl or (3C-6C) cycloalkyl, which alkyl, alkenyl and cycloalkyl groups can optionally be substituted with one or more halogens.

2. A compound according to claim 1, having the formula II:

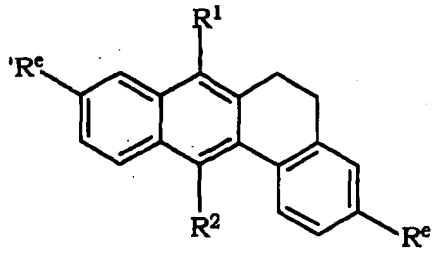


Formula II

wherein,
one of R^a or R^b is $'R^e$;
R^e and $'R^e$ are OH, optionally independently etherified or esterified;
Z is $-C(R^3,'R^3)-$ or $-C(R^4,'R^4)-C(R^5,'R^5)-$, wherein R^3, $'R^3$, R^4, $'R^4$, R^5, and $'R^5$, independently are H, (1C-4C)alkyl, (2C-4C)alkenyl or (3C-6C)

R^e and $'R^e$ are OH, optionally independently etherified or esterified;
R^1 and R^2 independently are H, halogen, CN, optionally substituted aryl, (1C-4C)alkyl, (2C-4C)alkenyl, (2C-4C)alkynyl or (3C-6C)cycloalkyl, which alkyl, alkenyl, alkynyl and cycloalkyl groups can optionally be substituted with one or more halogens;
Z is $-C(R^3,'R^3)-$ or $-C(R^4,'R^4)-C(R^5,'R^5)-$, wherein R^3, $'R^3$, R^4, $'R^4$, R^5, and $'R^5$, independently are H, (1C-4C)alkyl, (2C-4C)alkenyl or (3C-6C) cycloalkyl, which alkyl, alkenyl and cycloalkyl groups can optionally be substituted with one or more halogens.

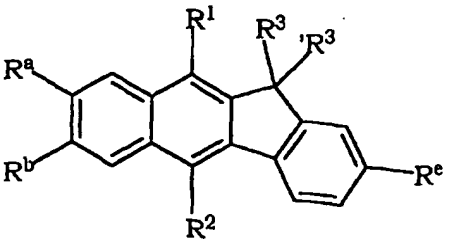
7. A compound according to claim 6, having Formula VII



Formula VII

wherein,
R^e and $'R^e$ are OH, optionally independently etherified or esterified;
R^1 and R^2 independently are H, halogen, CN, optionally substituted aryl, (1C-4C)alkyl, (2C-4C)alkenyl, (2C-4C)alkynyl or (3C-6C)cycloalkyl, which alkyl, alkenyl, alkynyl and cycloalkyl groups can optionally be substituted with one or more halogens.

8. A compound according to claim 6, having Formula VIII



Formula VIII

wherein,

one of R^a or R^b is $'R^e$;

R^1 and R^2 independently are H, halogen, CN, optionally substituted aryl, (1C-4C)alkyl, (2C-4C)alkenyl, (2C-4C)alkynyl or (3C-6C)cycloalkyl, which alkyl, alkenyl, alkynyl and cycloalkyl groups can optionally be substituted with one or more halogens;

R^3 and $'R^3$ independently are H or CH^3.

9. A compound according to claim 8, characterised in that R^a is $'R^e$, R^b is H, R^3, $'R^3$ are H or methyl, R^1 or R^2 is H and the other of R^1 or R^2 is halogen, CN, optionally substituted aryl, (1C-4C)alkyl, (2C-4C)alkenyl, (2C-4C)alkynyl or (3C-6C)cycloalkyl, which alkyl, alkenyl, alkynyl and cycloalkyl groups can optionally be substituted with one or more halogens.

10. A compound according to anyone of claim 1-9, characterised in that R^1 is halogen or fluorine substituted methyl.

11. A compound according to any one of claim 1-10 for use as a medicine

12. The use of a compound according to any one of claims 1-10 for the manufacture of a medicine for use in estrogen-receptor related treatments.

13. A pharmaceutical composition comprising a compound according to any one of claim 1 – 10.

INTERNATIONAL SEARCH REPORT

Int — ional Application No
PCT/EP 01/03187

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D221/18 C07C33/36 C07C33/38 C07C33/50 C07C43/21
C07C43/225 A61K31/047 A61K31/09 A61K31/473 A61P5/30

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07D C07C

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)
EPO-Internal, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

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Y	BEISLER J A: "POTENTIAL ANTITUMOR AGENTS. 1. ANALOGS OF CAMPTOTHECIN" JOURNAL OF MEDICINAL CHEMISTRY, AMERICAN CHEMICAL SOCIETY. WASHINGTON, US, vol. 14, no. 11, 1971, pages 1116-1118, XP001010519 ISSN: 0022-2623 page 1117, compounds 8 to 13; table I	1-7, 11-13

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[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

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Date of the actual completion of the international search	Date of mailing of the international search report
27 August 2001	04/09/2001

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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

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